Investigating barriers to tamoxifen adherence in women with breast cancer

Moon, Zoe Emma

Awarding institution:
King's College London

King's College London

Institute of Psychiatry, Psychology and Neuroscience

Health Psychology Section

Investigating barriers to tamoxifen adherence in women with breast cancer

By

Zoë Moon

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Abstract

Up to 50% of Breast Cancer Survivors (BCS) do not take tamoxifen as prescribed, which increases the risk of recurrence and mortality. Few psychosocial predictors of non-adherence have been identified and no published studies have described interventions to improve tamoxifen adherence. The aims of this PhD were to examine barriers to tamoxifen adherence in BCS and to develop a psychoeducational intervention to improve adherence. To address limitations with previous research, this PhD used the Common Sense Model (CSM) and the Theory of Planned Behaviour (TPB) as a framework for investigating non-adherence. A systematic review found few consistent predictors of non-adherence and highlighted a need for more research on modifiable factors. A qualitative study showed that adherence was related to the beliefs patients hold about tamoxifen and how they weigh these beliefs up against their side effects (n=32). In a large questionnaire study (n=777), components from the CSM and the TPB explained between 17% and 46% of the variance in non-adherence. Unintentional non-adherence was reported more frequently than intentional non-adherence but was harder to explain.

Women within their first year of treatment were sent follow up questionnaires at 3, 6 and 12 months (n=345). Reported rates of non-adherence increased significantly over time, as did perceived intensity of side effects. Results identified severable variables associated with non-adherence: ethnicity, employment status, necessity/concerns differential and perceived behavioural control. Both models provided excellent discrimination between adherent and non-adherent women. A psychoeducational self-management booklet was developed and was trialled in a small study, which supported the feasibility and acceptability of the intervention (n=41). Significant improvements were seen to variables associated with adherence, such as side effects, medication beliefs and self-efficacy for managing symptoms.

The results from these studies highlight factors associated with tamoxifen non-adherence, which can be used clinically to identify patients at risk of non-adherence, and as the basis for interventions to improve adherence. Initial testing of a psychoeducational self-management intervention showed promising results. Combining constructs from both the CSM and the TPB provided the best understanding of non-adherence. Future research should apply this combined model to medication adherence in other conditions.

Table of Contents

Abstract 2
List of Figures 7
List of Tables 8
Acknowledgements 9
Abbreviations 10
1. Introduction to Breast cancer 11
1.1. Chapter overview 11
1.2. Structure of the breast and breast cancer 11
1.2.1. Structure of the breast 11
1.2.2. Classification of breast cancer 11
1.2.3. Staging 13
1.3. Incidence, mortality and survival 15
1.3.1. Incidence 15
1.3.2. Survival 15
1.3.3. Recurrence 16
1.4. Risk factors and causes of breast cancer 16
1.4.1. Age 16
1.4.2. Family history 16
1.4.3. Hormones 16
1.4.4. Other risk factors 17
1.5. Treatment 18
1.5.1. Surgery 18
1.5.2. Chemotherapy 18
1.5.3. Radiotherapy 19
1.5.4. Ovarian Ablation 19
1.5.5. Biological therapy 19
1.5.6. Adjuvant hormone therapy 20
1.6. Tamoxifen 20
1.6.1. Efficacy of tamoxifen 20
1.6.2. Side effects of tamoxifen 22
1.7. Living with breast cancer survivorship 26
1.7.1. Psychological impact 26
1.7.2. Impact on fertility 27
1.8. Summary 27
2. Medication adherence and persistence: theoretical perspectives and methodological considerations 29
2.1. Chapter overview 29
2.2. Non-adherence to medications 29
2.2.1. Defining non-adherence 29

2.2.2. Impact and rates of medication non-adherence 30
2.2.3. Measuring non-adherence 31
2.2.4. Factors affecting medication non-adherence 34
2.3. Non-adherence to tamoxifen 37
2.3.1. Extent of non-adherence to tamoxifen 37
2.3.2. Impact of non-adherence to tamoxifen 39
2.4. Models of non-adherence 40
2.4.1. Common Sense Model of Illness Representations 41
2.4.2. Theory of Planned Behaviour 50
2.4.3. Comparison of models 53
2.5. Overview of thesis 55
3. Systematic Review of barriers and facilitators of hormone therapy adherence and persistence 57
3.1. Chapter overview 57
3.2. Published paper 58
3.3. Update to published paper 93
3.4. Summary 95
4. A qualitative study to explore the experiences of breast cancer survivors taking tamoxifen 97
4.1. Chapter Overview 97
4.2. Published paper 99
4.3. Summary 123
5. Modification of the illness perceptions questionnaire for use in breast cancer survivors 125
5.1. Chapter Overview 125
5.2. Published paper 126
5.3. Summary 150
6. More than just side effects: the role of clinical and psychological factors in non-adherence to tamoxifen 151
6.1. Chapter Overview 151
6.2. Published paper 152
6.3. Summary 178
7. Factors related to the experience of menopausal symptoms in women prescribed tamoxifen 181
7.1. Chapter Overview 181
7.2. Published paper 182
7.3. Summary 200
8. Psychosocial predictors of non-adherence to tamoxifen in breast cancer survivors: A longitudinal analysis 201
8.1. Background 201
8.1.1. Aims and hypotheses 204

8.2. Methods 205
8.2.1. Participants 205
8.2.2. Procedure 205
8.2.3. Statistical analysis 205
8.3. Results 207
8.3.1. Response rate 207
8.3.2. Difference between responders and non-responders 208
8.3.3. Participant demographics 210
8.3.4. Missing data 210
8.3.5. Changes in adherence over time 212
8.3.6. Changes in psycho-social variables over time 215
8.3.7. Latent growth modelling (LGM) 221
8.3.8. Model fit 231
8.3.9. Sensitivity analysis for cut-offs on the MARS 232
8.4. Discussion 232
9. Development of a psychoeducational intervention to support women taking tamoxifen 240
9.1. Chapter overview 240
9.2. Introduction 240
9.3. Framework for intervention development 242
9.3.1. Stage one: Needs Assessment 244
9.3.2. Stage two: Identify Intervention Objectives 245
9.3.3. Stage three: Theory based methods and practical strategies 246
9.3.4. Stage four: Develop intervention 251
9.4. Developing and piloting the intervention content 254
9.5. Intervention content 256
9.5.1. Section 1: What is tamoxifen? 256
9.5.2. Section 2: How to take tamoxifen 258
9.5.3. Section 3: Side effects of tamoxifen 260
9.5.4. Section 4: Support 261
9.6. Summary 262
10. Feasibility and acceptability of a psychoeducational intervention for breast cancer survivors prescribed tamoxifen 263
10.1. Chapter overview 263
10.1.1. Study aims 263
10.2. Methods 264
10.2.1. Ethical approval 264
10.2.2. Design 264
10.2.3. Participants 264
10.2.4. Procedure 266

10.2.5. Outcome measurements 266
10.2.6. Intervention 268
10.2.7. Statistical analysis 269
10.3. Results 269
10.3.1. Missing data 269
10.3.2. Recruitment and uptake 269
10.3.3. Study retention and participation 272
10.3.4. Participant demographics 273
10.3.5. Baseline adherence rates 273
10.3.6. Side effects 274
10.3.7. Relationship between adherence and covariates at baseline 274
10.3.8. Changes to adherence 275
10.3.9. Changes to illness and treatment beliefs 276
10.3.10. Changes to side effects, quality of life and distress 276
10.4. Discussion 278
11. Overall discussion 284
11.1. Chapter overview 284
11.2. Summary of aims and main findings 284
11.3. Contributions to the literature 286
11.4. Theoretical implications 287
11.4.1. The Common Sense Model of Illness Representations 287
11.4.2. The Theory of Planned Behaviour 291
11.4.3. Comparison of the CSM and the TPB 292
11.5. Clinical implications 295
11.6. Strengths and limitations 297
11.7. Future work 301
11.8. Overall conclusions 302
References 304
Appendices 367
Appendix A 367
Appendix B 369
Appendix C 374
Appendix D 395
Appendix E 397
Appendix F 398
Appendix G 399
Appendix H 401
Appendix I 409
Appendix J 412

List of Figures

Figure 2.1 Five interrelating factors associated with medication adherence (Sabate, 2003). 34
Figure 2.2 Common Sense Model (Leventhal et al., 1992) 43
Figure 2.3 Extended Common Sense Model with addition of medication beliefs (Horne & Weinman, 2002) 47
Figure 2.4 Theory of Planned Behaviour 51
Figure 8.1 Flowchart showing participant retention 209
Figure 8.2 Graph showing adherence rates across different patterns of retention 212
Figure 8.3 Graph showing mean MARS scores from baseline to 12 months 214
Figure 8.4 Graph showing percentage of women classed as non-adherent over time 215
Figure 8.5 Changes in illness perceptions (risk of recurrence, breast cancer consequences, tamoxifen consequences, cure) over time 218
Figure 8.6 Changes in illness perceptions (coherence, identity, personal control, treatment control, emotional representations) over time 219
Figure 8.7 Changes in necessity beliefs and concerns over time. 220
Figure 8.8 Changes in TPB variables over time 220
Figure 8.9 Latent growth model for non-adherence scores over time. 221
Figure 8.10 Expected and observed values for non-adherence, based on the linear (top graph) and quadratic (bottom graph) models 222
Figure 8.11 Expected and observed values for intentional non-adherence, based on the linear (top graph) and quadratic (bottom graph) models. 226
Figure 8.12 Expected and observed values for unintentional non-adherence, based on the linear (top graph) and quadratic (bottom graph) models. 229
Figure 9.1 Intervention Mapping framework. Adapted from Bartholomew et al. (1998) ... 244
Figure 9.2 Intervention Mapping framework. Adapted from Bartholomew et al. (1998) ... 247
Figure 9.3 Diagram showing mechanism of action for tamoxifen 257
Figure 10.1 Flowchart showing recruitment from NHS sites. 270
Figure 10.2 Flowchart showing recruitment from previous study. 271
Figure 10.3 Flowchart showing participation retention through study 272

List of Tables

Table 1.1 TNM Staging System of breast cancer 14
Table 1.2 Numbered staging system for breast cancer 14
Table 1.3 Breast cancer survival rates 15
Table 1.4 Side effects associated with tamoxifen and AIs 23
Table 2.1 Ilness perceptions 42
Table 8.1 Differences between responders and non-responders 211
Table 8.2 Baseline demographic and clinical characteristics of participants 213
Table 8.3 Changes to psychosocial variables over time 217
Table 8.4 Model fit statistics for linear and quadratic models for overall non-adherence 222
Table 8.5 Effects of covariates on the intercept and slope of non-adherence 224
Table 8.6 Results of the multivariate LGM testing variables from the CSM 224
Table 8.7 Results of the multivariate LGM testing variables from the TPB 225
Table 8.8 Model fit statistics for linear and quadratic models for intentional non-adherence 225
Table 8.9 Effects of covariates on the intercept and slope for intentional non-adherence 227
Table 8.10 Results of the multivariate LGM testing variables from the CSM: Intentional non-adherence 228
Table 8.11 Results of the multivariate LGM testing variables from the TPB: Intentional non-adherence 228
Table 8.12 Model fit statistics for linear and quadratic models for unintentional non-adherence 228
Table 8.13 Effects of covariates on the intercept and slope for unintentional non-adherence 230
Table 8.14 Results of the multivariate LGM testing variables from the CSM: Unintentional non-adherence 230
Table 8.15 Results of the multivariate LGM testing variables from the TPB: Unintentional non-adherence 231
Table 8.16 ROC analyses to compare predictive ability of CSM and TPB 231
Table 9.1 Key determinants of non-adherence (and non-persistence) identified by the needs assessment 246
Table 9.2 Key behaviour change strategies used in intervention 253
Table 9.3 Feedback on the intervention materials from patient representatives 255
Table 9.4 Intervention sections 256
Table 10.1 Demographic characteristics of participants 274
Table 10.2 Side effects reported by participants at baseline 275
Table 10.3 Changes to adherence scores pre-and post-intervention 276
Table 10.4 Changes to illness and treatment beliefs pre-and post-intervention 277

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Abbreviations

Abbreviation	Meaning
AI	Aromatase Inhibitor
ANOVA	Analysis of Variance
BCS	Breast Cancer Survivor
BMQ	Beliefs about Medicines Questionnaire
CBT	Cognitive Behavioural Therapy
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CNS	Clinical Nurse Specialist
COM-B	Capability, Opportunity and Motivation model of Behaviour
CSM	Common Sense Model
DCIS	Ductal Carcinoma in Situ
DFS	Disease Free Survival
EFA	Exploratory Factor Analysis
EM	Educational Materials
ER+	Oestrogen Receptor Positive
FACT-ES	Functional Assessment of Cancer Therapy – Endocrine Symptoms
FCR	Fear of Cancer Recurrence
HADS	Hospital Anxiety and Depression Scale
HBM	Health Belief Model
HCP	Healthcare Professional
HFNS	Hot Flushes/Night Sweats
HRT	Hormone Replacement Therapy
HT	Hormone Therapy
IBD	Inflammatory Bowel Disease
IM	Intervention Mapping
IPQ	Illness Perception Questionnaire
IPQ-BCS	Illness Perception Questionnaire – Breast Cancer Survivors
IPQ-R	Revised Illness Perception Questionnaire
LCIS	Lobular Carcinoma in Situ
LGM	Latent Growth Model
MARS	Medication Adherence Rating Scale
MEMS	Medication Event Monitoring System
MRC	Medical Research Council
NCF	Necessity Concerns Framework
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NPT	Normalisation Process Theory
OC	Oral Contraceptives
PBC	Perceived Behavioural Control
PR+	Progesterone Receptor Positive
QOL	Quality of Life
RCT	Randomised Controlled Trial
RMSEA	Root Mean Square Error of Approximation
SERM	Selective Estrogen Receptor Modulator
SIMS	Satisfaction with Information about Medication Scale
SSRI	Selective Serotonin Reuptake Inhibitor
TLI	Tucker Lewis Index
TPB	Theory of Planned Behaviour
WHO	World Health Organisation

1. Introduction to Breast cancer

1.1. Chapter overview

To give context for the body of work presented in the thesis, this chapter will provide an overview of breast cancer and tamoxifen. The clinical characteristics of breast cancer will be described, followed by the aetiology and epidemiology of the disease. Treatment options will then discussed, with a focus on hormone therapy and tamoxifen. The psychological impact of breast cancer and breast cancer survivorship will then be summarised.

1.2. Structure of the breast and breast cancer

1.2.1. Structure of the breast

The female breast is made up mostly of adipose or fatty tissue. It also contains a complex network of lobes and ducts. A healthy breast contains up to 20 lobes, which are made up of smaller lobules, where milk is produced in women who are nursing. Lobes and lobules are connected to the nipple by thin tubes known as milk ducts. Breast cancer usually forms within these lobes and ducts. It occurs when cells divide and grow in irregular and uncontrolled ways. Every time a cell is multiplied, the DNA is copied. Sometimes this DNA is copied with errors which change the instructions for how a cell should multiply. These errors are usually corrected by repair genes, however when they do not get corrected, the error is reproduced and replicated in new cells. Over time, these abnormal cells multiply and develop into a lump called a tumour.

The lymphatic system plays an important role in fighting infections and bacteria. It is also responsible for destroying abnormal cells such as cancer cells. The lymphatic system consists of lymph nodes, small bean-shaped collections of immune cells, and lymph vessels. Lymph vessels are very thin tubes found throughout the body. They carry a liquid called lymph, which fights infections and destroys damaged or abnormal cells. When a cancer cell breaks away from a tumour, it will travel to other parts of the body through the lymphatic system or the blood stream. Most of these cancer cells will be destroyed by the body, but some may travel to become tumours elsewhere. If breast cancer cells are found in nearby lymph nodes, such as under the armpit, it is an indication that the cancer has broken away from the tumour and is therefore more likely to spread to other parts of the body (Breast Cancer Now, 2017).

1.2.2. Classification of breast cancer

Breast cancer is a collection of different diseases which have distinct histopathological features, genetic variability and prognostic outcomes (Vargo-Gogola & Rosen, 2007). A

World Health Organisation (WHO) report estimates that there are seventeen distinct histological types of breast cancer (Ellis et al., 2003). Breast cancer which has not spread beyond the breast or lymph nodes is known as primary breast cancer. Cancers which have spread to other organs in the body are known as secondary or metastatic cancer. If a breast cancer has the ability to spread to other organs it is classed as invasive breast cancer. Some breast cancers carry cellular receptors. For example, around three quarters of breast cancers are oestrogen receptor positive (ER+), which means that cancer cells in these tumours require oestrogen for survival (Harrell et al., 2007). These cancer cells are stimulated by oestrogen to divide and grow. Around two thirds of ER+ breast cancers are also progesterone receptor positive (PR+). The best prognosis is found for tumours which are both ER+ and PR+ as the tumour is less aggressive and there are more treatment options (Dunnwald, Rossing, & Li, 2007). The tumour can also be assessed for the percentage of cells in the tumour which test positive for hormone receptors. This is known as an Allred score and can range from 0-8, where a score of 8 indicates that there are more receptors and a score of 0 indicates hormone receptor negative cancer (Dabbs, 2014). A higher score indicates that there will be greater benefit of Hormone Therapy (HT).

Cancer cells can also be tested for HER2 status. Cancers which are HER2 positive have high levels of HER2 genes, which causes over-expression of the HER2 protein. This then causes increased proliferation of cancer cells. Approximately 15-25% of breast cancers are HER2 positive (Piccart-Gebhart et al., 2005). These cancers tend to grow at a faster rate and have a higher rate of recurrence. Breast cancers which are triple negative, i.e. that are not positive for any of the above receptors, have a worse prognosis as they cannot benefit from targeted therapy. Around 15% of invasive breast cancers are triple negative (Cleator, Heller & Coombes, 2007).

1.2.2.1. DCIS/LCIS

Ductal Carcinoma in Situ (DCIS) is an early form of breast cancer which occurs when breast cancer cells are contained within the breast ducts and have not spread into other breast tissue. This type of cancer is non-invasive, but may become invasive if left untreated. Lobular Carcinoma in Situ (LCIS) is a condition where abnormal cells are found in the lobules of the breast. Whilst LCIS is not seen as cancer and does not require treatment, women with LCIS are at increased risk of developing breast cancer in the future (Cancer Research UK, 2017a).

1.2.2.2. Invasive cancer

The most common type of breast cancer is invasive ductal cancer, accounting for 50-80% of all cases (Ellis et al., 2003). This is a broad term which encompasses different subtypes of

breast cancer. Invasive ductal cancer originates in the cells of the ducts and spreads into surrounding breast tissue. Women with invasive ductal cancer may experience changes in the shape or size of the breast or changes to the skin or nipple. Invasive lobular cancer occurs when cancer cells that originated in the lobes have spread to surrounding breast tissue. Invasive lobular cancer is less common than invasive ductal cancer, accounting for around 5-15% of all cases (Cristofanili et al., 2005).

1.2.3. Staging

Breast cancers are assigned a stage at diagnosis which determines the treatment plan and prognosis. The TMN staging system takes into account the size of the tumour (T), whether it has spread to the lymph nodes (N), and if it has spread elsewhere in the body (M). Each of these factors is considered individually and an overall stage is given (Table 1.1). For example, if a tumour was under 2cm with no evidence of spreading, the cancer would be staged as T1 N0 M0.

Another common staging system is the numbered staging system which also takes into account the tumour size, nodal involvement and amount of metastasis. Stage I cancers are less than 2cm, have spread to 0-3 auxillary lymph nodes and have not spread elsewhere in the body. Stage II/III breast cancers have not metastasised but can involve larger tumours and more lymph node involvement. Stage IV breast cancer has metastasised. Stages I – IIIA are known as early breast cancer (Table 1.2).

Cancer cells can also be assigned a grade based on examination under a microscope. Lower grades indicate cells which look like normal breast cells. Higher grade cancers grow faster than lower grade cancers. The stage and grade of the tumour will affect the treatment course and the prognosis. Doctors can input the stage and grade of the cancer into computer programs (e.g. Adjuvant! Online, PREDICT, Nottingham Prognostic Indicator) to provide statistics for prognosis and guide treatment options.

Table 1.1 TNM Staging System of breast cancer

Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Cancer cells are only growing in the most superficial layer of tissue (DCIS/LCIS)
T1	Tumour <20mm
T2	Tumour >20mm but <50mm
T3	Tumour >50mm
T4	Tumour of any size with direct extension to the chest wall and/or the skin
Nodes	
NX	Lymph nodes cannot be evaluated
N0	Nearby lymph nodes do not contain cancer
N1	Cancer has spread to 1-3 axillary lymph nodes
N2	Cancer has spread to 4-9 axillary lymph nodes, or has spread to internal mammary lymph nodes
N3	Cancer has spread to 10 or more lymph nodes under the arm, clavicle or collarbone, or has spread to internal mammary nodes and axillary nodes, or has spread to lymph nodes above the clavicle
Metastasis	
M0	No distant cancer spread
M1	Distant metastasis were found

Source: http://emedicine.medscape.com/article/2007112-overview

Table 1.2 Numbered staging system for breast cancer

Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T0	N1	M0
	T1	N1	M0
IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

Source: http://emedicine.medscape.com/article/2007112-overview

1.3. Incidence, mortality and survival

1.3.1. Incidence

Breast cancer is the most common cancer in the UK and is the third most common cause of cancer-related death (Cancer Research UK, 2017b). There were 46,417 new cases of breast cancer diagnosed in England in 2014 (Office for National Statistics, 2016). Almost four out of five of these cases are diagnosed in women aged 50 and over (Office for National Statistics, 2012). Across 2006-2009, 41% of diagnosed breast cancers were stage I, 45% Stage II, 9% Stage III and 5% were Stage IV (Lyratzopoulos et al., 2012). Incidence rates in the UK have risen by 72% since the mid-1970s (Cancer Research UK, 2014a). This may be caused by widespread screening programs detecting early cancers such as DCIS which may never go on to cause any problems for the patient (Bleyer & Welch, 2012; DeSantis, Ma, Bryan, & Jemal, 2014). It may also be a result of lifestyle changes, as increased alcohol consumption, higher body fat and use of hormone replacement therapy (HRT) are all related to increased risk of breast cancer (Parkin, Boyd & Walker, 2011; World Cancer Research Fund/American Institute for Cancer Research, 2016; Writing Group for the Women's Health Initiative, 2002). Increased rates may also be a result of women having children later in life or having fewer children (DeSantis et al., 2014).

1.3.2. Survival

There are 11,600 breast cancer deaths in the UK each year, which equates to around 32 women per day (Cancer Research UK, 2014a). Due to improvements in screening and treatment, more women than ever are surviving breast cancer and death rates have fallen by 40% in the last 30 years (Cancer Research UK, 2014a). Table 1.3 shows the average survival rates for one, five and ten years post diagnosis. The prognosis is dependent on the type and stage of breast cancer. For example, triple negative breast cancer is associated with a worse prognosis and higher rates of mortality because it does not respond to targeted therapy (Dent et al., 2007). Prognosis is improved for women who have ER+ or PR+ tumours (Dunnwald et al., 2007).

Table 1.3 **Breast cancer survival rates**

	Overall	Stage I	Stage II	Stage III	Stage IV
Survival rates for one year	98%	100%	100%	97%	67%
Survival rates for five years	85%	90%	70%	50%	13%
Survival rates for ten years	77%	85%	60%	40%	10%

Source: http://www.cancerresearchuk.org/about-cancer/breast-cancer/survival

1.3.3. Recurrence

The chance of a recurrence remains high, even after treatment. Cancer which reoccurs in the breast area is known as a local recurrence. The cancer can also spread beyond the breast and lymph nodes in the arm into the tissues and lymph nodes around the chest, neck and breastbone, which is known as a regional recurrence. These cancer cells are more likely to spread elsewhere in the body (Susan G. Komen, 2017). Cancer which spreads to other organs or to the bones is known as secondary or metastatic breast cancer. Cancer cells can spread through the bloodstream or lymph fluid and become trapped in different organs and tissues. Risk of recurrence is highest within the first two years after diagnosis (Saphner, Tormey, & Gray, 1996), but may still be substantial up to twenty years after diagnosis (Early Breast Cancer Trialists' Collaborative, 2005).

1.4. Risk factors and causes of breast cancer

1.4.1. Age

As people age, there are greater opportunities for replication errors when cells divide. Therefore, the risk of breast cancer increases as women get older (Cancer Research UK, 2014a). Most breast cancers occur in women over 50, and the incidence of breast cancer is extremely low before age 30 (Singletary, 2003).

1.4.2. Family history

Having a first degree relative (mother, sister or daughter) diagnosed with breast cancer approximately doubles the risk of developing breast cancer (Nelson et al., 2012; Pharoah, Day, Duffy, Easton, & Ponder, 1997). The National Institute for Health and Care Excellence (NICE) recommends that women who have a first degree relative who was diagnosed under the age of 40, or who have two first degree relatives with breast cancer should visit the breast clinic for assessment. However, whilst family history is an important risk factor, only 3% of breast cancer is linked to a known breast gene. The main genes identified to date are BRCA1 and BRCA2. Women who have these genes have a 45-90% lifetime risk of developing breast cancer. Additionally, TP52 and PTEN genes have also been shown to increase the risk of breast cancer, but are much rarer (McPherson, Steel, & Dixon, 2000).

1.4.3. Hormones

As some cancer cells are stimulated by oestrogen, high levels of oestrogen can increase the risk of breast cancer. For example, women who start menstruating early (<11 years) may have a higher risk of breast cancer due to increased oestrogen exposure (Collaborative Group on Hormonal Factors in Breast Cancer, 2002a). Furthermore, nulligravid women, or

women who have children later in life, may also have a higher risk as their oestrogen exposure has not been interrupted by pregnancy (Ma, Bernstein, Pike, & Ursin, 2006). The Collaborative Group on Hormonal Factors in Breast Cancer (2002a) found the longer women breast feed, the more they are protected against breast cancer, with the risk of breast cancer decreasing by 4% for every 12 months of breast feeding, and by 7% for each birth. The oral contraceptive (OC) pill has also been linked to breast cancer risk. The International Agency for Research on Cancer (IARC) classified current or recent use of combined oestrogen-progestogen OCs as a cause of breast cancer (IARC, 2014). Research shows that current users of OCs have a slightly but significantly higher risk of breast cancer than non-users (Gierisch et al., 2013; Nelson et al., 2012). However, the breast cancers diagnosed in OC users tend to be less advanced than those diagnosed in never users. Furthermore, whilst OCs may be a risk factor, breast cancer incidence is low in women on OCs as they tend to be younger, and therefore OCs are only linked to an estimated 1% of female breast cancers in the UK (Parkin, 2011). The increased risk of breast cancer declines after women stop using OCs and is diminished entirely after ten years (Collaborative Group on Hormonal Factors in Breast Cancer, 1996).

Several large studies such as the Million Women study in the UK and the Women's Health Initiative Randomised Controlled Trial in the US have found increased risk of breast cancer for women taking HRT (Beral, 2003; Writing Group for the Women's Health Initiative Investigators, 2002). Women who took continuous HRT for five years had a 24% higher risk of invasive breast cancer than women who were taking placebos. It has been estimated that 3% of all breast cancers in the UK are attributed to HRT use (Parkin, 2011). However, the Million Women Study showed that past users of HRT are not at increased risk of breast cancer.

1.4.4. Other risk factors

Other potential risk factors include breast density, weight, diet and alcohol consumption. The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) have classed body fatness as a risk factor for post-menopausal breast cancer and greater weight at birth as a probable cause of pre-menopausal breast cancer (WCRF/AICR, 2016), with an estimated 9% of all breast cancers in the UK being linked to excess body weight (Parkin et al., 2011). Meta-analyses have shown that the risk of breast cancer is increased for women who drink more units of alcohol per day (Allen et al., 2009; Collaborative Group on Hormonal Factors in Breast Cancer, 2002b). Parkin et al. (2011) linked an estimated 6% of breast cancer incidences in the UK to alcohol consumption.

1.5. Treatment

Treatment options vary significantly depending on the type and stage of the cancer, the size of the tumour, the grade of the cells and the patient's menopausal status. Computer programs can be used to assess how each treatment will affect the risk of recurrence. Ultrasounds are usually conducted before surgery to examine the lymph nodes. If results look abnormal, a fine needle aspiration is used to extract fluid or cells for testing to determine if the cancer has spread into the lymph nodes. Women with locally advanced breast cancer may be given chemotherapy or HT before surgery to shrink a tumour, which is known as neoadjuvant treatment. Adjuvant treatment is given after surgery to kill any remaining cancer cells and reduce the risk of a recurrence.

1.5.1. Surgery

Most patients receive surgery to remove the cancerous cells and reduce the likelihood of the cancer recurring or spreading. Patients can either undergo a lumpectomy, where the tumour is removed with a border of healthy tissue, or a mastectomy, where the whole breast is removed. Some patients may also have a quadrantectomy, which is where a quarter of the breast tissue is removed, but this is less common. Quadrantectomy and lumpectomies are known as breast-conserving surgery and are much less invasive than mastectomies. After the lumpectomy, tissue samples are sent to a pathologist to be examined. This will determine if there are cancer cells in the healthy tissue. If cancer cells are found in the tissue then more surgery may be needed. Lymph nodes can also be assessed during surgery using a sentinel lymph node biopsy. If cancer is found in the lymph nodes then a second operation will be conducted to remove the lymph nodes.

Survival and recurrence rates are comparable between patients treated with breast-conserving surgery plus radiation and with mastectomy (Fisher et al., 2002; van Dongen et al., 2000). Breast-conserving surgery is often preferable as it preserves some breast tissue and has a reduced impact on the patient. However, mastectomies are still performed, especially if the tumour is large, if the lump is the middle of the breast, if there is more than one area of cancer in the breast or if there are areas of DCIS in the breast. Women who undergo a mastectomy are offered breast reconstruction.

1.5.2. Chemotherapy

Chemotherapy can be offered as adjuvant or neoadjuvant treatment. It works by using cytotoxic drugs to prevent cancer cells from dividing and growing. Several large trials have shown that neo-adjuvant chemotherapy is effective in shrinking tumours, thus allowing the majority of patients to be treated with breast-conserving surgery rather than mastectomy

(Bonadonna et al., 1998; Fisher et al., 1997). A large meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has shown that adjuvant chemotherapy can reduce breast cancer mortality by about one third, with greater benefits found in women with lymph node metastases (EBCTCG, 2012). The benefit is also greater in younger women than older women, perhaps due to the suppressive effects of chemotherapy on ovarian function in younger pre-menopausal women (EBCTCG, 2005). Multi-agent chemotherapy (polychemotherapy) has been shown to be more effective than single agent based therapy (EBCTCG, 2012). It is most often given intravenously, but oral delivery is increasingly common (Neuss et al., 2013). Chemotherapy can stop the ovaries from producing oestrogen, which may stimulate an early menopause in pre-menopausal women.

1.5.3. Radiotherapy

Radiotherapy uses radiation to destroy cancer cells. It is usually delivered post-surgery in order to remove any remaining cancer cells and reduce the risk of a recurrence. A large meta-analysis of over 10,000 patients found that radiotherapy can halve the rate of recurrence over ten years and reduce the rate of mortality by about a sixth (EBCTCG, 2011a). Treatment with breast-conserving surgery and radiotherapy is shown to be equally as effective as a total mastectomy (Fisher et al., 1985; Litière et al., 2012).

1.5.4. Ovarian Ablation

Ovarian ablation is a treatment given to pre-menopausal women with early stage breast cancer. It refers to any treatment used to remove the ovaries or stop the ovaries from working, thus reducing levels of oestrogen in the body. Ovarian ablation may involve treatment with a hormonal drug such as Goserelin (Zoladex), which stops the production of oestrogen from the ovaries. This is usually a reversible procedure. Women can also have an operation known as an oophectomy to remove their ovaries or can receive radiation on the ovaries to permanently stop them working.

1.5.5. Biological therapy

Biological therapies work by changing the way cancer cells interact, which stops them from sending signals to divide and grow. The most common treatment is Trastuzuman (Herceptin) which is used in women with HER2 positive cancer. Herceptin, which binds to the HER2 receptors to inhibit cancer cell growth, can significantly reduce the risk of recurrence and breast cancer mortality (Piccart-Gebhart et al., 2005) Current recommendations are for a 12 month course of Herceptin, initiated alongside chemotherapy.

1.5.6. Adjuvant hormone therapy

Adjuvant hormone therapy (HT) is prescribed to women with hormone receptor positive breast cancer. It is a systemic treatment, which means it acts to control any remaining cancer cells across the body. The two main types of adjuvant HT are aromatase inhibitors (AIs) and selective oestrogen receptor modulators (SERMs). SERMs work by blocking the oestrogen receptor and preventing oestrogen from stimulating cancer cells. The most commonly prescribed SERM is tamoxifen. Other SERMs such as raloxifene are used in the prevention of breast cancer in healthy women but are not usually used to treat the disease. AIs (i.e. anastrazole, letrozole, exemestane) stop the production of oestrogen in post-menopausal women. HT is one of the most effective systemic treatments for breast cancer and given the prevalence of ER+ breast cancer, researchers believe that HT has a greater global impact than any other treatment in cancer medicine (Aguilar et al., 2010; Sledge et al., 2014).

1.6. Tamoxifen

Tamoxifen is usually taken as a 20mg tablet once a day. It is converted by the liver into the active form hydroxytamoxifen by an enzyme called cytrochrome P450 isoenzyme 2D6 (CYP2D6). Once converted, hydroxytamoxifen binds to the oestrogen receptor but does not activate the receptor and therefore does not stimulate the cells to divide and grow.

1.6.1. Efficacy of tamoxifen

Tamoxifen was initially synthesised as a drug for contraception before scientists realised its potential in breast cancer. The first trial of tamoxifen was conducted at the Christie Hospital in 1970 and the drug was approved in the UK in 1972. In 1998, the EBCTCG conducted a meta-analysis of 55 studies (n=37,000) and found that five years of adjuvant tamoxifen could halve the risk of recurrence in ER+ breast cancers (proportional recurrence reductions=47%, *SD*=3). This meta-analysis was updated in 2005, with results showing that the benefits of tamoxifen clearly persist for 15 years post diagnosis (EBCTCG, 2005). The most recent meta-analysis showed that for women with ER+ breast cancer, five years of tamoxifen could reduce breast cancer mortality by about a third (RR=0.70, $p<0.001$; EBCTCG , 2011b). Across all time periods, the reduction in rate of recurrence was about 39% (RR=0.61, $p<0.001$). The benefits of tamoxifen are found regardless of age, menopausal status and use of chemotherapy, but are only shown in women with ER+ disease (EBCTCG, 1998).

As well as being used in breast cancer survivors (BCS), tamoxifen is also licensed as a prophylaxis in women at high risk of developing breast cancer. The National Surgical Adjuvant Breast and Bowel Project conducted a randomised clinical trial to investigate the

effectiveness of tamoxifen at preventing breast cancer (NSABP P-1 trial). Results showed that the incidence of ER+ breast cancer was reduced by 57% after seven years of tamoxifen (Fisher et al., 2005), with an incidence rate for invasive breast cancer of 43 women per 1000 in the placebo group and 25 per 1000 in the tamoxifen group. The International Breast Cancer Intervention Study 1 (IBIS-I) recruited 7154 high risk women across 9 countries and randomised them to five years of tamoxifen or placebo. At the 16 year follow up, the risk of developing breast cancer was significantly reduced in the tamoxifen group (HR=0.71, 95% CI=0.60-0.83, p<.001; Cuzick et al., 2015).

Until recently, tamoxifen was the gold standard treatment for pre and post-menopausal women (Palmieri, Patten, Januszewski, Zucchini, & Howell, 2014). However, AIs are now being considered as first line treatment for post-menopausal women. Due to their mechanism of action, AIs can only be prescribed in post-menopausal women and therefore tamoxifen remains the recommended treatment in pre-menopausal women. Whilst pre-menopausal women produce oestrogen through their ovaries, this ceases once women reach the menopause. In post-menopausal women, oestrogen is still produced in other parts of the body, where it is converted from androgens by the enzyme aromatase. AIs work by preventing aromatase from converting androgens to oestrogen, and therefore lowering circulating oestrogen levels. They cannot be prescribed in pre-menopausal women as they do not stop the ovaries from producing oestrogen.

The first trial to compare AIs with tamoxifen was the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, which randomised 9366 postmenopausal women to receive either anastrazole or tamoxifen. Results showed anastrazole was both more effective and less toxic than tamoxifen (Baum et al., 2002). This trial was followed by the BIG I-98 and TEAM trials, which compared five years of AIs, five years of tamoxifen and a switch protocol (2-3 years of tamoxifen followed by 2-3 years AIs) in postmenopausal women. As with the ATAC study, Disease Free Survival (DFS) was higher in the AI group than the tamoxifen group but there was no evidence for superiority between the switch protocol and five years of tamoxifen (The Breast International Group 1-98 Collaborative Group, 2005; van de Velde et al., 2011). In a meta-analysis of almost 10,000 women, Dowsett et al. (2009) found that two to three years of tamoxifen followed by 2-3 years of AIs was more effective than five years of tamoxifen. The results of these studies have led to NICE and the American Society for Clinical Oncology recommending AIs as primary treatment for post-menopausal women (Burstein et al., 2010; NICE, 2009). Tamoxifen is recommended if AIs are not tolerated or are contraindicated and remains the standard of care in pre or peri-menopausal women. Pre or peri-menopausal women can also be offered ovarian suppression alongside tamoxifen (Burstein et al., 2016).

More than half of recurrences in ER+ breast cancer occur after five years (Johnston & Yeo, 2014) and therefore there is a need to identify ways to protect women for longer. Until recently, there was no indication that HT should be prescribed for longer than five years. This was based on the results of the Scottish Adjuvant Tamoxifen trial and the NSABP-14 trials, which showed no additional benefit for women taking tamoxifen beyond 5 years (Fisher et al., 1996; Stewart, Prescott, & Forrest, 2001). However, whilst the NSABP-14 had a relatively large sample size (n=2892), the Scottish Adjuvant Tamoxifen trial was smaller, with only 342 women being randomised in the follow up study. Two recent large studies have challenged the assumption that there are no benefits for continuing tamoxifen treatment for a further five years. In the Adjuvant Tamoxifen; To Offer More? (aTTom) trial (n=6953), ten years of tamoxifen was associated with a 25% reduction in risk of recurrence and a 23% reduction in mortality (Gray et al., 2013). The Adjuvant Tamoxifen Longer Against Shorter (ATLAS) trial (n=6846), conducted across 36 countries, also showed superiority of ten years of tamoxifen for women with ER+ breast cancer, with reductions in both recurrence and mortality (Davies, Pan, Godwin, Gray, & Peto, 2012). Combining the results of both studies shows significant reductions in mortality (RR=0.85, 95% CI=0.77-0.94, p=.001; Palmieri et al., 2014). The results of these trials are now being translated into clinical practice, with pre-menopausal women being offered another five years of tamoxifen, or a switch to an AI, after the first five years of treatment (Burstein et al., 2014; NICE, 2013a). Several studies have also assessed the effectiveness of extended AI treatment after five years of tamoxifen (Goss, 2006; Jakesz et al., 2007; Mamounas, 2001). Results show reduced recurrence, higher DFS and overall survival in those taking extended AIs compared to those taking placebo. The clear benefits of an additional 5 years of letrozole over placebo led to the MA.17 trial being un-blinded after 2.4 years and all patients being offered extended letrozole treatment (Goss et al., 2005).

1.6.2. Side effects of tamoxifen

Tamoxifen and AIs have similar side effects profiles, as they both work by depriving the body of oestrogen. However, incidence of certain side effects does differ between treatments. The side effects listed by drug manufacturers are shown in Table 1.4. Analysis of the ATAC trial showed that bone fractures were more common in the anastrazole group, whereas endometrial cancer was more common in the tamoxifen group (Buzdar et al., 2006). Vasomotor symptoms, difficulty with bladder control and gynaecological symptoms are more severe in patients treated with tamoxifen whereas musculoskeletal pain and vaginal symptoms are worse in AIs (Ganz et al., 2016). Cardiac failure and other cardiovascular events were higher in AIs (Cella & Fallowfield, 2008). Decreased bone density, arthralgia, osteoporosis and fracture risk are all more common with AIs (Blaha et al., 2009; Regan,

Price, Giobbie-Hurder, Thurlimann, & Gelber, 2011). Conversely, tamoxifen exerts a beneficial influence on bone metabolism in post-menopausal women. However, whilst AIs are associated with poorer bone health, they lack the life threatening adverse events seen with tamoxifen, such as thromboembolic complications and endometrial cancer.

Tamoxifen acts as an agonist in the endometrium and can therefore cause gynaecological symptoms such as vaginal bleeding or discharge, or increased risk of endometrial cancer (Blaha et al., 2009). The endometrial cancer risk is a significant concern for patients, but is far outweighed by the benefits of taking tamoxifen in terms of reducing the risk of breast cancer recurrence. The incidence of endometrial cancer in the UK is very low to begin with: there were only 28 cases per 100,000 women in 2014 (Cancer Research UK, 2014b).

Table 1.4 Side effects associated with tamoxifen and AIs

	Side effects of tamoxifen	Side effects of anastrazole (AI)
Very common (may affect more than 1 in 10)	Hot flushes, vaginal bleeding/discharge, skin rash, nausea, fluid retention, tiredness	Hot flushes, skin rash, nausea, headache, joint pain, arthritis, osteoporosis, feeling weak
Common (may affect up to 1 in 10 people)	Anaemia, light-headedness, headache, hair loss, cataracts, leg cramps, muscle pain, genital itching, thickening of the womb lining, allergic reactions, blood clots, confusion, eye problems	Hair loss, muscle pain, allergic reactions, loss of appetite, tiredness, vaginal dryness, vaginal bleeding, diarrhoea, vomiting, bone pain
Uncommon (may affect up to 1 in 100)	Cancer of the endometrium, pancreatitis, inflammation of the lungs, blood disorders	Hepatitis, hives
Rare (may affect up to 1 in 1000)	Abnormal menstrual cycle, endometriosis, vaginal polyps, skin rashes, cancer of the womb, damage to nerve cells in optic nerve, liver disorders	Skin rash, inflammation of blood vessels
Very rare (may affect up to 1 in 10,000)	Cutaneous lupus erythematosus, skin blistering, thrombophlebitis	Skin blistering, angioedema

Source: https://www.medicines.org.uk/emc/PIL.32536.latest.pdf, https://www.medicines.org.uk/emc/PIL.25780.latest.pdf

Therefore the increased risk does not translate to large numbers of women. The increased risk is also only shown in post-menopausal women. The NSABP prevention trials have showed no statistically significant difference in endometrial cancer incidence in the tamoxifen or placebo groups for women aged below 50 (Fisher et al., 1998). Furthermore, in a recent study, tamoxifen only led to increased endometrial cancer in cases where there were womb abnormalities at baseline (Potkul et al., 2016). If a woman had a normal scan when being prescribed tamoxifen, there was no increased risk of endometrial cancer.

Thromboembolic complications such as strokes, deep vein thrombosis and pulmonary embolisms are also more common with tamoxifen than with AIs. The ATAC trial showed that at 68 months, the risk of venous thromboembolic complications was elevated in the tamoxifen group (5%) compared to the anastrazole group (3%; Buzdar et al., 2006).

Hot flushes and night sweats (HFNS) are a result of withdrawal of oestrogen and are common in both women taking AIs and women taking tamoxifen (Harris et al., 2002; Moon, Hunter, Moss-Morris, & Hughes, 2016). Whilst HFNS are a symptom of the menopause and therefore may still occur in healthy women, women with breast cancer are five times more likely than age matched controls to experience these symptoms and are also more likely to experience longer, more frequent and more severe HFNS (Carpenter, Johnson, Wagner, & Andrykowski, 2002; Harris, Remington, Trentham-Dietz, Allen, & Newcomb, 2002; Marino et al., 2014). Additionally, women who take tamoxifen are twice as likely to experience HFNS as other BCS and are more likely to report severe HFNS (Harris et al., 2002; Morales et al., 2004). Many patients report weight gain whilst taking tamoxifen, but as several studies found no differences in weight gain between patients in the tamoxifen and placebo arms of trials (Day et al., 1999; Nyrop, Williams, Muss, & Shachar, 2016), it is unclear if weight gain is a side effect of tamoxifen treatment. Cognitive deficits, or "chemo brain" is a well acknowledged side effect of chemotherapy (Raffa et al., 2006), and some recent studies have suggested that a similar cognitive decline is also associated with tamoxifen treatment (Bakoyiannis, Tsigka, Perrea, & Pergialiotis, 2016; Chen et al., 2014). These deficits affect attention, concentration, verbal and visual memory, language and motor skills. However, the majority of studies investigating cognitive function in HT are underpowered and have flawed designs (Zwart, Terra, Linn, & Schagen, 2015) and therefore further research is needed to establish the effects of HT on cognitive function. Some patients also report low mood or changes in mood whilst taking tamoxifen (Ganz, Rowland, Desmond, Meyerowitz, & Wyatt, 1998; Moon et al., 2016). It is unclear if this is related specifically to tamoxifen or to breast cancer survivorship. Two studies have shown no differences in rates of depression between women taking tamoxifen and women taking a placebo, suggesting that tamoxifen is not associated with depressed mood (Day et al., 1999; Love, Cameron, Connell, & Leventhal, 1991).

Several studies suggest that HT side effects may be valuable markers of treatment efficacy. Women who reported vasomotor symptoms in the ATAC trial were less likely to experience a recurrence (Cuzick, Sestak, Cella, Fallowfield, & Grp, 2008). In another study, hot flushes were a stronger predictor of breast cancer specific outcomes than age, hormone receptor status or stage of cancer at diagnosis (Mortimer et al., 2008). Fontein et al. (2013) found that women who experienced specific adverse events had better DFS and overall survival than

women with non-specific or no adverse events. These effects may be due to CYP2D6 activity, where side effects are an indication that the drug is being metabolised. However, the relationship between side effects and treatment efficacy may be driven by a common third factor which both increases reporting of adverse events and improves clinical outcomes (Pritchard, 2013). For example, women who are more focused on their health and who engage more in healthy behaviours, may be more likely to notice and report side effects, as well as being more likely to have improved clinical outcomes.

Research with women taking HT has shown that the most bothersome side effects for patients are hot flushes, weight gain, insomnia and joint symptoms (Garreau, Delamelena, Walts, Karamlou, & Johnson, 2006). These symptoms have a negative impact on emotional, physical and social functioning and are associated with anxiety and sleep problems in BCS (Boehm et al., 2009; Garreau et al., 2006; Hunter & Chilcot, 2013). Management options for these symptoms are limited and physicians often underestimate the effects of symptoms on patients and fail to help women to manage symptoms (Fellowes, Fallowfield, Saunders, & Houghton, 2001; Leonard, Lee, & Harrison, 1996; van Londen et al., 2014b). HFNS can be treated with HRT, but this is contraindicated in ER+ BCS due to the potential increased risk of breast cancer. Selective Serotonin Reuptake Inhibitors (SSRIs) can reduce hot flush severity, but some also interfere with the breakdown of tamoxifen. NICE recommends that venlaflaxine is used in the treatment of HFNS in BCS as it does not interfere with tamoxifen. However, many BCS are keen to avoid additional medications which likely have side effects and instead state a preference for natural treatments (Hunter et al., 2004). One non-pharmacological treatment is Cognitive Behavioural Therapy (CBT) for HFNS, which is recommended by NICE guidelines (NICE, 2015). A six week program of group CBT has been proven to be effective at reducing HFNS problem rating and improving social/physical functioning in a large RCT of BCS (Mann et al., 2012). Management options for other symptoms are also lacking. There is some evidence that yoga might reduce general pain, muscle aches and physical discomfort in BCS taking HT, but long term follow up is needed to establish how long these effects last (Carson, Carson, Porter, Keefe, & Seewaldt, 2009; Peppone et al., 2015). To treat vaginal dryness and dyspareunia, non-hormonal lubricants and vaginal moisturisers can be used but oestrogen treatments should be avoided. Juraskova et al. (2013) have shown some promise for a treatment composed of olive oil, vaginal exercise and moisturiser to relieve dyspareunia and improve sexual function and Quality of Life (QOL).

1.7. Living with breast cancer survivorship

1.7.1. Psychological impact

The psychological impact of breast cancer often persists long after treatment has finished. Whilst patients do not tend to see themselves as still having breast cancer, the vast majority see themselves as survivors; a process which is seen as continuing across the lifespan (Bowman, Deimling, Smerglia, Sage, & Kahana, 2003; Jagielski, Hawley, Corbin, Weiss, & Griggs, 2012). Some BCS report feeling like they are left in an ambiguous state between being ill and being healthy (Powers, Gullifer, & Shaw, 2016) and others feel permanently "branded" by the disease (McKenzie & Crouch, 2004).

Most women are focussed purely on survival during treatment, and the emotional impact of the cancer may not become apparent until remission. Feelings of uncertainty, vulnerability and ambivalence are common at the end of treatment (Lethborg, Kissane, Burns, & Snyder, 2000). Support from healthcare professionals stops almost immediately after primary treatment in the UK, and in some cases, social support will also decrease once friends and family perceive things to be back to normal. Studies have shown that nearly half of patients experience depression or anxiety in the year after diagnosis (Burgess et al., 2005; Gold et al., 2016) and that around 15-24% still experience these symptoms up to four years after diagnosis (Bleiker, Pouwer, van der Ploeg, Leer, & Ader, 2000; Burgess et al., 2005; Cvetković & Nenadović, 2016). This psychological distress has been shown to impact on clinical outcomes; after controlling for known clinical and histopathological prognostic factors, low distress was predictive of longer DFS and overall survival (Groenvold et al., 2007).

Common psychological concerns for BCS focus on dating or relationships, body image and sexual dysfunction (Ganz et al., 1996). However, some of these concerns, such as sexual dysfunction, are associated with natural ageing and are also present in healthy post-menopausal women. Younger women are shown to have higher levels of distress than older women (Costanzo et al., 2007), which may be related to concerns regarding premature menopause, body image and infertility (Howard-Anderson, Ganz, Bower, & Stanton, 2012). Another psychological concern is the fear that the cancer will return. Up to 70% of BCS show clinical levels of Fear of Cancer Recurrence (FCR; Thewes et al., 2012). Coping with this FCR is often rated as an unmet need for cancer survivors (Stanton et al., 2005) and may be problematic for patients. It is associated with poor QOL (Koch et al., 2014), depressive symptoms (Deimling, Bowman, Sterns, Wagner, & Kahana, 2006) and more intrusive thoughts about illness (Simard, Savard, & Ivers, 2010). FCR remains stable across the survivorship trajectory (Simard et al., 2013) and is heightened in younger survivors

(Costanzo et al., 2007; Koch et al., 2014; Simard et al., 2013). Some researchers have identified unhelpful meta-cognitions which are linked to FCR in younger women, such as negative beliefs about worry and need for control over cognition (Thewes, Bell, & Butow, 2013). Beliefs that women hold about their illness and its treatment have also been shown to be associated with FCR in BCS taking HT (Corter, Findlay, Broom, Porter, & Petrie, 2013). As well as distress, persistent fatigue is also prevalent in BCS. Around one quarter to one third of BCS report fatigue at two to five years post diagnosis (Bower et al., 2006; Cella, Davis, Breitbart, & Curt, 2001; Servaes, Gielissen, Verhagen, & Bleijenberg, 2007). Post-cancer fatigue is related to increased depression, pain and sleep disturbance (Bower et al., 2000).

However, whilst some studies indicate heightened distress in BCS, others have found no differences in QOL between BCS and healthy controls (Ganz et al., 1998; Helgeson & Tomich, 2005) or show good adjustment in BCS (Costanzo et al., 2007). Many women also identify positive aspects from the cancer experience (Ganz et al., 1996). For example, women report growing as individuals and focussing more on the things which are deemed important (Hodgkinson et al., 2007). Furthermore, Deimling et al. (2006) found that whilst one third of BCS worried about a recurrence, their QOL was not dramatically compromised (Deimling et al., 2006).

1.7.2. Impact on fertility

Some women are unable to have children after treatment for breast cancer. Chemotherapy can cause amenorrhoea and infertility in pre-menopausal women. This amenorrhoea may be permanent or may reverse after treatment. Periods are more likely to re-start in women who are younger (<35 years). Women who do have periods after chemotherapy are still more likely to experience an early menopause as a result of the treatment. It is possible for pre-menopausal women to become pregnant whilst taking tamoxifen, as tamoxifen does not cause infertility, and may actually increase fertility. However, it can cause significant foetal abnormalities and therefore becoming pregnant whilst taking tamoxifen is not recommended. After tamoxifen treatment, women should be able to conceive, provided they have not naturally gone through the menopause during treatment.

1.8. Summary

This chapter has highlighted the high prevalence of breast cancer in the UK. Three quarters of these breast cancers are ER+ and can be treated with HT such as tamoxifen. The research described above highlights the clinical importance of taking tamoxifen. The research in this PhD will focus on women with ER+ breast cancer who are prescribed tamoxifen. This is particularly relevant given that tamoxifen is now being prescribed for up to ten years and to

women who are at high risk of developing breast cancer. There will be a focus on women who are within their first two years after primary treatment, in order to investigate how women cope with the treatment and how their perceptions and behaviours may change over time.

2. Medication adherence and persistence: theoretical perspectives and methodological considerations

2.1. Chapter overview

This chapter will provide a brief overview of research around medication adherence. It will first summarise the extent and impact of non-adherence across conditions and will review factors associated with non-adherence. It will then review methods for measuring non-adherence, before discussing the extent of non-adherence to tamoxifen specifically. Finally, two social cognition models (the Theory of Planned Behaviour and the Common Sense Model) will be discussed in the context of understanding medication adherence.

2.2. Non-adherence to medications

2.2.1. Defining non-adherence

The terms adherence and compliance are often used interchangeably. Compliance is defined as "*the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen*" (Cramer et al., 2008, page 44). This definition assumes that the patient is passive and does not actively agree to the treatment recommendations. Adherence, however, involves the patient taking a more active role in their treatment decisions. The World Health Organisation (WHO) define medication non-adherence as "*the extent to which a person's medication taking behaviour corresponds with agreed recommendations from a health care provider*" (Sabate, 2003, page 3). Adherence usually refers to the proportion of the medication the patient is taking, and non-adherence can refer to taking both more and less than the prescribed dosage, as well as not adhering to strict dosing and timing regimens. In addition to non-adherence, patients can also be non-persistent or they could not initiate treatment. The term non-persistence, or discontinuation, is used to describe patients who terminate treatment against their health care provider's advice before the recommended duration. Non-initiation refers to patients who are offered a treatment but decide not to begin treatment.

Non-adherence can be termed as intentional, where the patient makes a deliberate decision not to take their medication, or unintentional, where they may forget or not understand the instructions. Unintentional non-adherence tends to be reported more frequently than intentional non-adherence (Riegel & Dickson, 2016; Unni & Farris, 2011). However, this may be due to patients feeling more comfortable admitting to forgetting their medication than to deliberately not taking it (Atkins & Fallowfield, 2006). Furthermore, whilst intentional and unintentional non-adherence appear to be distinct concepts, there may be

significant overlap across the behaviours. If taking the medication is important to a patient, they will probably set up stringent routines in order to remember to take it (Clifford, Barber, & Horne, 2008). Therefore, patients who believe more strongly in the importance of their medication may be less likely to forget their medication as well as less likely to deliberately skip doses. Intentional and unintentional non-adherence are also not mutually exclusive. A patient could forget some doses or not follow the instructions properly, as well as deliberately skipping some doses to avoid side effects.

2.2.2. Impact and rates of medication non-adherence

Between 30% and 50% of all medication for chronic illness is not taken as prescribed (Sabate, 2003). Adherence in life threatening illnesses, such as cancer, is often assumed not to be a problem, due to the severity of the diagnosis. However, Lebovits et al. (1990) found that only 57% of oral chemotherapy was taken as prescribed in a sample of breast cancer patients. In a large review across illnesses, rates of medication non-adherence were highest in HIV, arthritis, gastrointestinal disorders and cancer (DiMatteo, 2004a). Optimum medication adherence is usually defined as 80%, but can be higher in some conditions such as HIV, where up to 95% is considered optimal (Osterberg & Blaschke, 2005).

Non-adherence has strong implications for global healthcare, as poor adherence can dramatically reduce the effectiveness of medications. Researchers have suggested that increasing adherence may have a greater impact on the health of the population than improvements in any specific medical treatment (Haynes, McDonald, Garg & Montague, 2002). For example, it has been estimated that better adherence to hypertension treatment could prevent 89,000 premature deaths a year in the US (Cutler et al., 2007). Implications of non-adherence include poor clinical outcomes, drug resistance and medications being presumed ineffective and discontinued or escalated. DiMatteo, Giordani, Lepper & Croghan (2002) conducted a meta-analysis of 63 studies examining the association between adherence to medical treatment and clinical outcomes. Results showed the odds of a good outcome were almost three times higher if the patient was adherent. However, the authors acknowledge that the studies were correlational and that there may therefore be a chance that instead of adherence influencing outcomes, clinical outcomes may influence adherence. Alternatively, both adherence and outcomes may be driven by a third variable such as life circumstances, personality or quality of health care.

As well as the significant clinical impact of non-adherence, there are also more general economic and societal costs. Non-adherence to medications can cause disease exacerbation or relapse, which results in increased hospital admissions and surgeries (Goodhand et al., 2013; Sokol, McGuigan, Verbrugghe, & Epstein, 2005). Wu et al. (2010) found that patients

with leukaemia who took less than 85% of the recommended dose of imatinib had higher inpatient costs, pharmacy costs and outpatient costs. This increase in healthcare service use results in costs of up to $100 billion a year in the US (Coambs et al., 1995; Osterberg & Blaschke, 2005). As well as direct healthcare costs, there are also indirect costs of non-adherence, such as disability payments and medically related absenteeism. For example, in the US, medication non-adherence in chronic conditions is associated with a higher number of days on short term disability or absent from work (Carls et al., 2012).

2.2.3. Measuring non-adherence

Medication adherence is difficult to measure and there is no gold standard measurement tool. One issue with assessing adherence is the Hawthorne effect, where participants may be more inclined to adhere if they know they are being monitored. Measurement methods tend to fall into two broad categories; objective measurements and subjective measurements. Objective measurements include biomarkers, electronic monitoring, pharmacy data and pill counts. Biomarkers in blood are often the most accurate way to measure if a drug has been ingested. However, this is a very costly method, it is intrusive to the patient, and it is not feasible for all medications. As tamoxifen has a long half-life (terminal elimination half-life 5-7 days), detection of the substance is not an accurate assessment of whether it has been taken recently. Furthermore, tamoxifen metabolism is complex and varies across individuals, which limits the utility of biomarkers as a measurement of adherence (Kisanga et al., 2004).

An alternative less obtrusive assessment is to count how many pills the patient has taken. One way of measuring this is using electronic monitoring, such as Medication Event Monitoring System (MEMS) caps, which record when the medication packet has been opened. However, MEMS caps only record when the medication was opened and not if it was actually taken. MEMS is also criticised for inducing the Hawthorne effect (Bruxvoort, 2015; Sutton et al., 2014). Ethically, patients must be made aware that their behaviour is being measured. There are also practical issues with using the MEMS cap; in a study of Anti-Retroviral Treatment adherence, 36% of participants reported that they did not use the MEMS cap consistently (Bova et al., 2005). However, researchers have shown that the Hawthorne effect is limited to 40 days (Deschamps et al., 2006) and that the benefits of MEMS outweigh the drawbacks (Sutton et al., 2014).

Prescription refill rates provide another measurement of how much medication the patient has taken. A medication possession ratio is calculated as the total days' supply of medication dispensed divided by the number of days that the patient should be taking the medication. Patients are usually classed as non-adherent if they take less than 80% of the prescribed dose, which is a somewhat arbitrary figure but is supported in Hormone Therapy (HT)

adherence, as < 80% adherence is associated with increased risk of mortality (Hershman et al., 2011). Discontinuation can be measured by identifying gaps in prescription refill rates, for example gaps of 30-180 days. However, prescription refill rates can only be used in settings where medications are covered by a single payer, and similarly to the MEMS cap, it isn't possible to tell if the patient has actually ingested the medication. Another method is pill counts, where the patient brings their pill packet to the researcher to count how many pills are in the container. This is a fairly simple and unobtrusive measure. However, patients can bias the measure by discarding pills before their appointment if they want to appear adherent (Osterberg & Blaschke, 2005). Furthermore, counting inaccuracies are common and can result in inflated levels of adherence (Matsui et al., 1994).

Subjective measurements include self-report measures such as questionnaires, interviews and diaries, which are simple, cheap and easy to administer. However, they often over-estimate adherence rates, most likely due to the patient wanting to please the researchers or because they fear chastisement (Berg & Arnsten, 2006; Bruxvoort et al., 2015). Recall bias might also be an issue if the patient is asked to recollect their previous medication taking behaviour over a significant period of time. Despite these problems, significant positive relationships have been found between patient reported adherence and objective adherence measures (Atkinson et al., 2016; Fairley, Permana, & Read, 2005; Shi et al., 2010). Questionnaire and diary methods tend to have higher concordance with objective measures than interviews (Garber, Nau, Erickson, Aikens, & Lawrence, 2004; Hawkshead & Krousel-Wood, 2007). Non-judgemental statements are added to some questionnaires in order to normalise non-adherence and reduce social desirability bias. Assurance that the results will not be passed on to clinic staff can also reduce social desirability bias (Williams, Amico, Bova, & Womack, 2013). Self-report measures have the advantage of allowing researchers to measure both intentional and unintentional non-adherence, which is not possible with the objective measures described above. Furthermore, whilst self-report measures may over-estimate adherence rates, they are likely to correctly identify those who report non-adherence (Sabate, 2003). Medical records can also be used to measure adherence, but they tend to correlate poorly with more objective measures, due to Healthcare Professionals (HCPs) over-estimating adherence rates. In one study, providers recognised non-adherence for less than half of patients whose pharmacy data indicated non-adherence (Meddings, Kerr, Heisler, & Hofer, 2012).

Much of the research on HT non-adherence utilises pharmacy refill rates to measure non-adherence, although there is also a large body of research using self-report measures. A simple yes/no self-report measure was shown to be associated with oestrogen serum levels in a sample of breast cancer patients (Brier et al, 2015), suggesting it provides a reliable

measure of adherence. Furthermore, Atkinson et al. (2016) found positive correlations between objective measures and self-report in oral anti-cancer medication adherence. However, others studies have shown poor correlation between self-report and more objective measures of HT adherence. In a group of 50 women taking Aromatase Inhibitors (AIs), all women reported high levels of adherence and yet the prescription data showed that only 69% of women were highly adherent (Ziller et al., 2009). Waterhouse, Calzone, Mele, and Brenner (1993) found self-reported adherence rates were significantly higher than those reported with MEMS, whilst Font et al. (2012) found low concordance between self-report, prescription refill rates and physician report for HT adherence.

As described above, there are several different approaches to the measurement of non-adherence, yet there are limitations associated with all these approaches and there is no gold standard measurement. Very few methods provide a completely accurate and reliable measurement of adherence, and the most reliable methods are costly and impractical to implement. The majority of research studies rely on prescription refill rates, self-report measures or electronic monitoring. Self-report measures are the most feasible, and whilst they are a subjective measure, steps can be taken to improve their reliability. These include using validated scales, reducing social desirability concerns, defining the adherence construct of interest and using optimised question response formats (Stirratt et al., 2015) Researchers have suggested that using multiple methods of measurement would improve accuracy, by overcoming some of the limitations associated with individual approaches (Lam & Freso, 2015; Lehmann et al., 2014; Sabate, 2003). A composite measure can also be created by encompassing these various measurements. This composite measure provided better prediction of HIV medication adherence than any individual method (Liu et al., 2001).

Another issue with the measurement of adherence is the categorisation of non-adherence or non-persistence, which varies significantly across studies, as does the terminology used to describe behaviours. The definition of non-adherence is slightly more consistent than persistence, with the majority of prescription refill studies categorising women as non-adherent if they collect prescriptions for less than 80% of their recommended doses. However, with self-report measures, it is not possible to obtain this information and the cut-offs for non-adherence vary, with some studies classifying participants as non-adherent if they report missing one dose in a week and others if they miss one dose a month. Validated questionnaires help to provide consistency as they specify guidelines for scoring the questionnaires. Recent efforts have been taken to obtain consensus on the terminology used to describe non-adherence behaviours (ABC Project Team, 2012). This consensus would aid with comparisons across studies.

2.2.4. Factors affecting medication non-adherence

Due to the significant clinical implications of non-adherence, a large amount of research has been conducted with the aim of identifying determinants of medication non-adherence. Over 700 individual factors have been investigated (Kardas, Lewek & Matyjaszczyk, 2013). The WHO grouped these into five main factors: 1) health system/health care professional related, 2) condition related, 3) patient related, 4) therapy related, 5) social/economic factors (Sabate, 2003; see Figure 2.1). They suggest that adherence is a multidimensional phenomenon which can be influenced by any of these factors. Health system factors include poor medication distribution services, short consultations and patient/physician relationship. Whilst there has been relatively little research investigating health system-related factors, some studies have investigated the effects of patient/physician relationship and physician communication on non-adherence. Several reviews have shown that non-adherence is associated with discordance between doctor and patient and poor patient physician communication (Jackson, Clatworthy, Robinson, & Horne, 2010; Osterberg & Blaschke, 2005). In a meta-analysis of 127 studies, there was a 19% higher risk of treatment non-adherence if the physician communicated poorly with the patient (Haskard Zolnierek & DiMatteo, 2009). Condition related factors, such as severity of symptoms or rate of disease progression, are not consistently related to medication adherence (Jackson et al., 2010; Khdour, Hawwa, Kidney, Smyth, & McElnay, 2012).

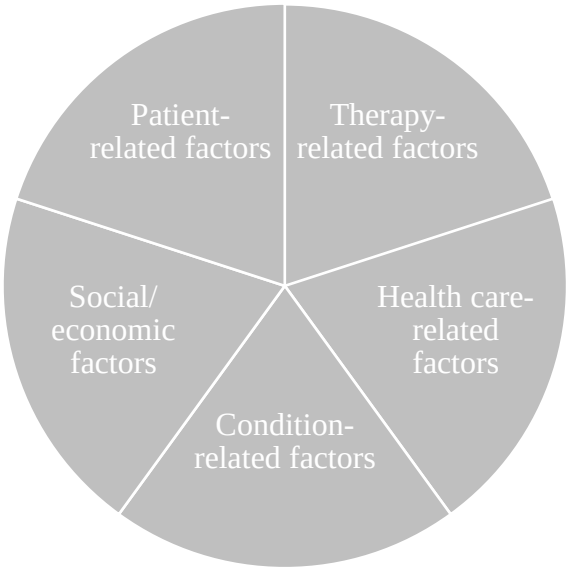

Figure 2.1 Five interrelating factors associated with medication adherence (Sabate, 2003)

Patient related factors include the patient's knowledge, beliefs, attitudes, expectations, mood or personality. A recent review found a small, positive association between health literacy and adherence (r=0.14; Miller, 2016). However, this relationship was strongest among non-medication regimes. Tae et al. (2016) found limited knowledge of the prescribed regimen was associated with non-adherence to medication in Inflammatory Bowel Disease (IBD). This is supported by studies showing that educational interventions can improve medication adherence (Clerisme-Beaty et al., 2011; Newman-Casey, Weizer, Heisler, Lee, & Stein, 2013). However, studies on the relationship between adherence and knowledge are often cross-sectional. Therefore, it is not possible to determine the direction of the relationship. Patients may be non-adherent because they have poor knowledge of their illness or treatment, or they may have poor knowledge because they are not interested in taking the medication. The relationship between adherence and self-efficacy is more consistent. A review found that of 19 studies testing a relationship between medication adherence and self-efficacy, 17 found a significant effect (Holmes, Hughes, & Morrison, 2014). There is also a fairly consistent relationship between treatment beliefs and medication adherence. Khdour et al. (2012) found that adherence to Chronic Obstructive Pulmonary Disorder medication was influenced more by patients' perceptions of their treatment and health than by demographic or disease factors. A meta-analysis showed that treatment adherence was significantly positively associated with patients' beliefs of the severity of their disease (DiMatteo, Haskard & Williams, 2007). Beliefs around medication necessity are also significantly associated with adherence, as are concerns about medications (Holmes et al., 2014). However, again, the majority of this research is correlational and cause and effect cannot be inferred.

Several studies have shown a link between depression and non-adherence, with depressed patients being up to three times more likely to be non-adherent to treatment recommendations (Berry, Blonquist, Hong, Halpenny, & Partridge, 2015; DiMatteo, Lepper & Croghan, 2000; Goodhand et al., 2013; Jackson et al., 2010; Khdour et al., 2012). However, Zwikker, van den Bemt, van den Ende and van Dulmen (2014a) reviewed the available literature on longitudinal associations between depression and medication non-adherence, and found the cross-sectional relationship was not maintained over time, maybe due to the low quality of evidence. Alternatively, the authors propose that depression correlates with non-adherence at the time, but has no effect on later non-adherence.

Some studies have found relationships between adherence and therapy related factors, such as increased number of doses per day or number of medications prescribed (Claxton, Cramer & Pierce, 2001; Vermiere, Heamshaw, Van Royen, & Denekens, 2001). However, in a review of medication adherence in IBD, Jackson et al. (2010) found no effects for treatment

related factors such as dosage, therapy duration or treatment history. Treatment side effects may also show an association with non-adherence, but these effects are not consistently found (Jackson et al., 2010; Partridge, Ades, Spicer, Englander, & Wickerham, 2007; Verbrugghe, Verhaeghe, Lauwaert, Beeckman, & Van Hecke, 2013).

Mixed results have been found for the effects of social or economic factors on adherence rates (Balkrishnan, 1998; Falagas, Zarkadoulia, & Pliatsika, 2008; Sabate, 2003). Demographic factors are also often found to be poor predictors of medication non-adherence (Greer, Pirl, Park, Lynch & Temel, 2008; Jackson et al., 2010; Vermiere et al., 2001). Some studies have found differences in adherence rates across different races, potentially due to cultural differences or social inequalities (Sabate, 2003). However, the effect between race and medication adherence is inconsistent (Jackson et al., 2010; Vermiere et al., 2001). Some studies have found that older (Verbrugghe et al., 2013) or younger age (Aggarwal & Mosca, 2010) is associated with increased non-adherence, but overall, the results are inconsistent and they vary substantially across conditions (Jackson et al., 2010; Sabate, 2003; Vermiere et al., 2001). Social support appears to show some associations with adherence. DiMatteo (2004b) conducted a meta-analysis across illnesses and found significant positive associations between practical social support and emotional support, family cohesiveness and treatment adherence. The results of this meta-analysis have been supported by a recent review (Kardas et al., 2013). However, the majority of research in the review was cross-sectional and there is wide variation in the definition and measurement of social support.

Despite the vast amount of research interest, no factors have been consistently highlighted as predictors of medication adherence (Dunbar-Jacobs & Rohay, 2016; Vermiere et al., 2001). It is likely that this lack of consistency is due to the fact that predictors of adherence vary across conditions and treatments. Whilst there are some common factors which are related to adherence across conditions, such as self-efficacy or medication beliefs, there are specific factors relating to individual medications and conditions. For example, age may be particularly relevant in tamoxifen adherence, as younger women may struggle more than older women with symptoms associated with early menopause. Furthermore, there are issues associated with the measurement of adherence. Dunbar-Jacobs and Rohay (2016) found that predictors of adherence vary significantly depending on the method used to measure adherence. For example, in patients with diabetes or rheumatoid arthritis, income was associated with MEMS adherence but not self-report adherence; whereas comorbidities were associated with self-report but not MEMS adherence.

2.3. Non-adherence to tamoxifen

2.3.1. Extent of non-adherence to tamoxifen

Systematic reviews have found adherence rates to HT ranging from 41-96% (Ayres, Baldoni, Borges, & Leira Pereira, 2014; Murphy, Bartholomew, Carpentier, Bluethmann, & Vernon, 2012). Hershman et al. (2010) analysed pharmacy records from 8769 women in the US and found that only half of patients took HT at the optimum schedule for the full duration of treatment. Kimmick et al. (2015) measured self-report HT adherence rates in 124 women and found 34% reported intentional non-adherence and 59% reported unintentional non-adherence. Research suggests that HT adherence rates fall across the course of treatment. For example, Partridge, Wang, Winer, and Avorn (2003), Seneviratne et al. (2015) and Wu, Stafkey-Mailey, and Bennett (2012) found that whilst around 77% of the sample were adherent in the first year of treatment, this fell to around 50% by the fouth or fifth year. As found in most conditions, adherence tends to be highest when measured by self-report and lower when measured with prescription refill data (Font et al., 2012; Grunfeld, Hunter, Sikka, & Mittal, 2005; Kimmick et al., 2009; Simon, Latreille, Matte, Desjardins, & Bergeron, 2014).

As well as high rates of non-adherence, studies also show that many women do not persist with HT treatment. However, the majority of studies do not measure both non-adherence and non-persistence, so it is not possible to determine the total proportion of women who are not taking their medication as prescribed. In a review of clinical trials, Chlebowski & Gellar (2006) found that 25% of women prematurely discontinued treatment. This estimate is likely higher in clinical practice, where non-persistence rates are higher than those seen in clinical trials (Hadji, 2010). Large studies in clinical practice have found that only 49-69% of women persist for the full treatment duration (Brito, Portela, & Vasconcellos, 2014b; van Herk-Sukel et al., 2010). The majority of studies find non-persistence rates of around 40-50% (Hadji et al., 2013b; Makubate, Donnan, Dewar, Thompson, & McCowan, 2013; McCowan et al., 2008; Owusu et al., 2008), which is supported by a meta-regression of 17 studies (Huiart, Ferdynus, & Giorgi, 2013). However, most of these studies do not have the information necessary to exclude patients with metastasis or patients who may have discontinued due to contraindications. There are a large number of reasons a patient could stop taking HT, and not all of these reasons should be classed as non-persistence. For example, a patient may have to stop treatment due to local recurrence or metastasis, or due to a life-threatening side effect such as thromboembolism. Alternatively, they may choose to stop taking it because they cannot see any benefits, or because they do not want to feel that they still have cancer. Guth, Myrick, Kilic, Eppenberger-Castori & Schmid (2012) propose

that the term non-persistence should only be used when there is a chance that the outcome could be modified, rather than in cases where discontinuation was inevitable. The majority of large pharmacy refill studies have not recorded the reasons why women discontinued, and are therefore unable to censor women who have been recommended by their physician to discontinue treatment (Barron, Connolly, Bennett, Feely, & Kennedy, 2007; Hadji et al., 2013b; Nekhlyudov, Li, Ross-Degnan, & Wagner, 2011; Ziller et al., 2009). It is likely, therefore, that the true incidence of non-persistence (where the outcome of non-persistence could have been prevented) is lower than the percentages reported in these studies. Other studies have attempted to censor women at time of death, BC recurrence and contralateral BC, but have reported unrealistically low rates of recurrence (1-5%), which may mean that they are not correctly identifying all patients who have had a recurrence (Hershman et al., 2010; Huiart et al., 2013). Guth et al. (2012) only classed women as non-persistent where the patient had a choice about stopping treatment, and excluded women with local/systemic breast cancer recurrence, those who were deceased and those who had contraindications for HT. They found a non-persistence rate of 17% over three years. However, as this study used self-report data, it likely under-estimated non-persistence levels.

One group of authors have provided non-persistence rates, as well as the non-adherence rates for those that persisted. Hershman et al. (2010) followed up 8769 women for 4.5 years and found that 2790 (32%) women discontinued treatment. Of those that continued, 28% were non-adherent (19% of the original total sample). These numbers show that of the original 8769 women, only 49% were fully adherent across the follow up period. Similar studies have found that 33-50% of the original sample took their medication as prescribed (Hershman et al., 2015; Hershman et al., 2014; Neugut et al., 2011). However, due to issues with classification and measurement of non-adherence/non-persistence, it is not possible to calculate the total proportion of non-adherent patients in many studies. For example, some papers on non-adherence are not clear as to whether non-persistent women were removed from analysis, or if they were classed as non-adherent. Others simply state that women who were non-persistent were removed from analysis, without providing the numbers of non-persistent women.

The majority of women who discontinue tamoxifen do so within the first year (Fink, Gurwitz, Rakowski, Guadagnoli, & Silliman, 2004; Huiart et al., 2012; Owusu et al., 2008; Ziller et al., 2009). One study found that 14.5% of patients had stopped taking tamoxifen within 90 days (Barron et al., 2007). Therefore, it is important to intervene and reduce non-persistence at the early stages of tamoxifen treatment. In addition to non-adherence and non-persistence, 7-30% of women who are prescribed tamoxifen do not initiate treatment, representing a large proportion of women who are not benefitting from HT and may be at

increased risk of recurrence and mortality (Cluze et al., 2012; Livaudais et al., 2012). This rises to 50% in a low income Medicaid-insured sample, perhaps due to side effects being particularly hard to manage for patients who are socioeconomically vulnerable or who have poor access to support (Wheeler et al., 2014). Some studies have compared tamoxifen adherence rates to adherence rates for AIs and have found superior adherence for tamoxifen (Brito, Portela, & de Vasconcellos, 2014a; Chirgrin et al., 2016). However, this may be due to the increased familiarity for tamoxifen in the general public and may reverse as AIs are prescribed more frequently.

Overall, research suggests that between 7-50% of women prescribed HT do not initiate treatment. Of women who have at least one prescription for HT, around 23-50% of women do not take it as prescribed. In addition to this, around 50% stop taking it prior to the prescribed duration. This suggests that a large proportion of women who could benefit from HT are not receiving these benefits. However, very few studies take all three behaviours into consideration and therefore it is not possible to get an estimate for the total proportion of women who are not taking HT as prescribed. Future research incorporating clear and concise measurements of the different behaviours would provide clear information of the scope of the problem.

2.3.2. Impact of non-adherence to tamoxifen

Non-adherence to oral cancer medications has significant implications (Hershman, 2016). The benefits of any medication are dramatically reduced if the drug is not taken as prescribed. Whilst clinical trials show substantial benefits of taking HT, these benefits may not be translated to clinical practice where adherence rates are much lower. Both non-adherence and non-persistence to HT have been associated with increased mortality (Chigrin et al., 2016; Hershman et al., 2011; Hsieh, Chen, Cheung, Chang & Yang, 2014; Makubate et al., 2013; McCowan et al., 2008; Valachis et al., 2016; Winn & Dusetzina, 2016). In one study, women who were non-persistent with HT had an almost threefold risk of recurrence (OR=2.88, CI=1.11-7.46; Barron, Cahir, Sharp & Bennett, 2013). Another study found that early discontinuation was associated with a 26% increase in all-cause mortality, and of the women that continued treatment, non-adherence was associated with a 49% increase in all-cause mortality (Hershman et al., 2011). When the cut off for non-adherence was raised from 80% to 90%, the detrimental effect of non-adherence on mortality was removed. This suggests that taking less than 80% of the prescribed dose is detrimental to survival, but that women taking above 80% of their medication are not at increased risk of mortality. However, whilst studies show an overall impact of adherence on risk of recurrence, the relationship varies significantly across individuals, as prognosis is dependent on a range of

tumour related clinical characteristics. For some individuals, tamoxifen may only reduce the risk of recurrence by a few percentage points, but for others the impact could be much greater. In addition to decreased survival, low adherence is also associated with a loss of quality adjusted life years, increased medical costs, higher hospitalisation rates and longer hospital stays (McCowan et al., 2013; Partridge, 2006; Waterhouse et al., 1993). However, the relationship between non-adherence and survival may not be causal. It could be driven by variables such as negative psychological outlook or other negative health behaviours, which may influence both adherence and DFS (Hershman, 2016). Studies have shown that adherence is associated with improved clinical outcomes, even when patients are adhering to a placebo (Coronary Drug Project Research Group, 1980). This supports the idea that there may be common factors which cause patients both to adhere to treatment and to have improved clinical outcomes.

2.4. Models of non-adherence

Social cognitive models help us to understand individual differences in health behaviour that demographic or clinical variables have largely failed to explain. By listing determinants of non-adherence which can be modified through intervention, these models also provide a blueprint for intervention development and enhance comparisons across studies. Previous interventions to improve adherence have been criticised for lacking a theoretical framework (Horne et al., 2005). Therefore, this PhD will use models of health behaviour as a framework for understanding non-adherence and to aid with development of an intervention to improve adherence. There are a range of social cognitive and psychological models which have been applied to health behaviours such as adherence. Some of the most commonly researched models include the Health Belief Model (HBM), the Theory of Planned Behaviour (TPB), the Transtheoretical Model of Change (TTM) and the Common Sense Model (CSM) (Holmes et al., 2014; Horne & Weinman, 1998). More recently, the COM-B model has been developed, but this has received less research attention. A brief overview of these models is provided below, followed by a detailed explanation of the models used within this thesis.

The HBM proposes that behaviour is driven by the perceived threat, perceived barriers and perceived benefits associated with the behaviour, as well as the individual's self-efficacy (Rosenstock, 1974). The model shows weak predictive power, mostly due to problems around testing the model, poor construct definition and weaknesses in predictive validity of the psychological components (Armitage & Connor, 2000; Harrison, Mullen & Green, 1992; Tanner-Smith & Brown, 2010). Several studies have shown that both the TPB and the CSM explain greater proportions of variance in health behaviour than the HBM (Bish, Sutton & Golombok, 2000; Gerend & Shepherd, 2012; Jones et al., 2014; Montanaro & Bryan, 2014).

The TTM is a stage based theory which suggests that individuals go through five stages of change before undergoing a health behaviour (Prochaska & DiClemente, 1982). The model has been the subject of extensive criticism (Adams & White, 2005; Armitage, 2009; West, 2005). Whilst the TTM may be a useful tool for identifying people at risk of non-adherence, it doesn't provide information for how to maintain adherence behaviours (Genberg et al., 2013; Horne & Weinman, 1998). A review by Bridle and colleagues showed limited evidence for interventions based on the TTM (Bridle et al., 2005). Furthermore, NICE guidance has suggested that the TTM should not be used in behaviour change interventions as it does not explain or predict behaviour change (NICE, 2014). The COM-B is a new model (Michie, van Stralen, & West, 2011), which brings together a range of key variables across different social cognition models. However, the model includes a large number of constructs and there is little guidance on selecting or measuring constructs.

Due to the criticisms associated with the models described above, it was felt that the CSM and the TPB had the best potential for understanding the complex behaviour of tamoxifen non-adherence. The decision to measure constructs from both models was based on suggestions from previous research stating that the use of multiple models of health behaviour could enhance both understanding of behaviour and effectiveness of interventions (Corda et al., 2010; Holmes et al., 2014; Michie et al., 2008; Nigg & Jordan, 2005). The CSM and the TPB appear to complement each other theoretically, as they reflect how a patient feels about their illness and their treatment, and how they feel about actually taking the medication. The models also cover some of the key elements which have been consistently highlighted as important determinants of non-adherence; self-efficacy, treatment beliefs and social support (DiMatteo, Haskard-Zolnierek & Martin, 2012; Holmes et al., 2014; O'Carroll et al., 2011). Furthermore, interventions based on these models have shown some success at improving adherence (Petrie et al., 2012; O'Carroll et al., 2013; Webb & Sheeran, 2006).

2.4.1. Common Sense Model of Illness Representations

The CSM proposes that patients are active problem solvers who will try and make sense of and to reduce a given illness or health threat (Leventhal, Diefenbach, & Leventhal, 1992). The model was developed from an earlier parallel processing model of fear, showing that cognitive and emotional information were processed as separate but interacting systems (Leventhal, 1970). The CSM suggests that patients engage in a system of parallel processing where they deal with both the perceived reality of the health threat (cognitive level) and the emotional reaction to the health threat (emotional level) (Diefenbach & Leventhal, 1996; Figure 2.2). Both of these processing systems involve the patient forming a representation,

selecting appropriate coping strategies and appraising the success of these coping strategies. There is a feedback loop within the model, where information from each of these stages is fed back to earlier stages. In the cognitive level, patients hold implicit common sense beliefs about their illness. These cognitive representations reflect how people perceive, understand and react to threats to health, and they guide the selection of coping behaviours which will attempt to resolve the health threat. Leventhal et al. (1992) identified five key perceptions that form cognitive representations; identity, timeline, consequences, causes and cure/control (see Table 2.1).

Table 2.1 Illness perceptions

Illness perceptions defined by Leventhal et al. (1992)	
Identity	The label given to the illness or symptom experiences
Causes	Beliefs around what caused the illness
Timeline	Perceived chronicity of illness
Cure/control	The extent to which the patient feels the illness can be cured or controlled
Consequences	Perceived consequences of the illness
Additional illness perceptions identified by Moss-Morris et al. (2002)	
Treatment control	Belief in the treatment or recommended advice
Personal control	Belief in personal control and self-efficacy
Timeline acute/chronic	Perceived chronicity of illness
Timeline cyclical	The extent to which symptoms come and go over time
Emotional representations	Assessment of the emotional responses generated by the illness
Coherence	The extent to which a patient's illness representation provides a coherent understanding of the illness

In parallel with cognitive processing, a health threat or illness can also evoke emotional reactions. For example, finding a lump might evoke strong feelings of fear and worry in some patients, whereas others might not have a strong emotional reaction, or may feel a different emotion such as anger or sadness. These emotional responses will feed into the selection of coping actions, both to control the illness threat and to regulate emotions (Leventhal et al., 2012). The cognitive and emotional processing arms are highly interactive, with emotions influencing illness cognition and vice versa (Cameron & Moss-Morris, 2010). For example, worry can promote rumination and cause people to be hypervigilant to symptoms, and low mood can increase reporting of physical symptoms (Salovey & Birnbaum, 1989). Hagger & Orbell (2006) showed that health threats such as abnormal cancer screening results can cause a range of emotional responses, such as anxiety, distress, guilt or sadness, and that these emotional responses are related to both cognitive and emotional representations of the illness. However, little attention has been paid to the emotional processing dimension of the model (Cameron & Jago, 2008).

The CSM is a dynamic model and the relationships between concepts are bi-directional. A fundamental premise of the CSM is that selection of coping behaviours, such as visiting the doctor, taking aspirin or resting, will be driven by the patient's illness representation. The outcomes of these coping behaviours are then appraised in terms of their success of managing the illness or health threat. This appraisal may lead to potential changes in illness perceptions.

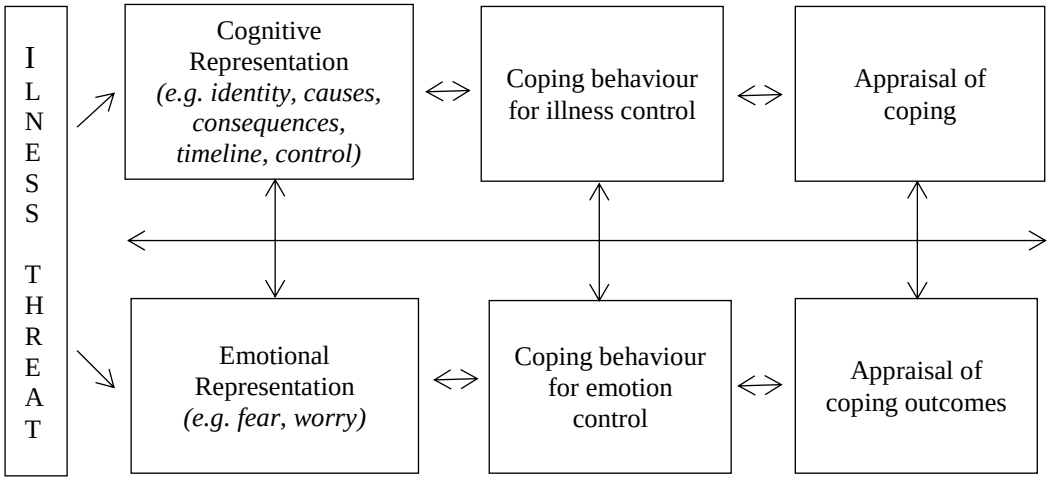

Figure 2.2 Common Sense Model (Leventhal et al., 1992)

For example, a patient may assume they have a mild headache and choose to drink water or take paracetamol to cope with the illness. If these coping strategies do not work, and the headache persists, the patient might modify their illness perceptions towards something more serious and long lasting. This may then lead to alternative coping strategies, such as visiting the GP. Illness representations, coping styles and appraisal can also be updated based on changes in somatic experiences or if the patient obtains new information, for example from the media or friends (Leventhal et al., 1992). As medication adherence is a potential coping behaviour, the CSM assumes that it should be influenced by the patient's perception of their illness and whether it makes sense for them to take a medication, based on these perceptions (Leventhal, Phillips, & Burns, 2016).

The CSM believes that there are several heuristics individuals use to make sense of illnesses. One of these is the symmetry rule, where patients expect to experience symptoms when they feel ill. Asymptomatic conditions such as hypertension or prophylactic medications therefore violate the symmetry rule. This is also likely the case in BCS taking tamoxifen, as there are no symptoms to be controlled. If the patient is not experiencing any symptoms, they may assume they are not ill. Non-adherence in these cases is a common-sense application of the symmetry rule (Diefenbach & Leventhal, 1996). Therefore, in chronic asymptomatic conditions, we may see different relationships between illness perceptions and adherence

than we would in illness models where the medication is actively controlling symptoms (Leventhal et al., 2016). This discrepancy between the acute representation and the demands of a chronic condition help to explain why people do not adhere to their medication.

The Illness Perceptions Questionnaire (IPQ) was developed to measure and quantify cognitive representations of illness (Weinman, Petrie, Moss-Morris & Horne, 1996). It measures the following perceptions: identity; causes; timeline beliefs; consequences and cure/control. The IPQ has been used countless times to assess the impact of cognitive representations on a range of health outcomes (Horne & Weinman, 2002; Murphy, Dickens, Creed & Bernstein, 1999; Rutter & Rutter, 2002; Scharloo et al., 1998). The questionnaire was revised several years later in order to improve the internal consistency of some subscales and to increase the scope of the measure (Moss-Morris et al., 2002). This Revised Illness Perceptions Questionnaire (IPQ-R) improved issues relating to the cure/control and timeline subscales (Table 2.1). Factor analysis showed that the cure/control dimension actually loaded onto two separate components; treatment control and personal control. The timeline scale was modified to include cyclical beliefs which were not included in the original scale. Finally, emotional representations and coherence were added to the questionnaire. Emotional representations form a key component of the CSM and yet were not assessed with the original IPQ. Illness coherence reflects the extent to which a patient's illness representation provides a coherent understanding of the illness. The revised scale was validated in a sample of 711 patients across eight illness groups. It showed good internal and test-retest reliability and sound discriminant group and predictive validity. The authors recommend that the scale is modified for use in different illness contexts, due to the unique characteristics of different illnesses (Moss-Morris et al., 2002). A shortened eight-item IPQ has also been developed for clinical use (Broadbent, Petrie, Main & Weinman, 2006). Whilst the IPQ-R shows good psychometric properties and demonstrated relationships with various clinical outcomes, including survival (Chilcot, Wellsted & Farrington, 2010; French, Cooper & Weinman, 2006; Jopson & Moss-Morris, 2003; Mann, Ponieman, Leventhal, & Halm, 2009; Whittaker, Kemp, & House, 2007), several issues with the measurement have been identified.

Think-aloud studies have shown that patients can struggle to answer questions on the IPQs (McCorry, Scullion, McMurray, Houghton, & Dempster, 2013b; van Oort, Schroder, & French, 2011). There is a need to establish the face validity of the questionnaires before they are applied to different illnesses. Simply changing the word '*illness'* to the specific illness is likely to be an insufficient modification (McCorry et al., 2013b). There are likely to be other issues with the questionnaire, such as in illnesses where patients may not have overt symptoms or may experience side effects from treatment. Without adaptation for different

illnesses, overall scores on IPQ subscales are not sufficient for informing intervention development and may not be particularly informative (French &Weinman, 2008; Phillips, Leventhal, & Burns, 2017). The IPQ-R has also been criticised for being a static measure which fails to represent the dynamic nature of the CSM (Leventhal et al., 2016; Phillips et al., 2017). Novel approaches to assessing illness perceptions include having patients draw their illness (Broadbent, Petrie, Ellis, Ying, & Gamble, 2004) or using materials such as clay to produce a representation of their cancer (Harrow, Wells, Humphris, Taylor, &Williams, 2008).

Illness representations have been studied extensively as predictors of non-adherence. Identity (Llewelyn, Miners, Lee, Harrington, & Weinman, 2003), consequences (Brewer, Chapman, Brownlee, & Leventhal, 2002; Horne & Weinman, 2002), timeline (Byer & Myers, 2000; Van der Have, 2016), causes (Chen, Tsai, & Chou, 2011), emotional responses (Daleboudt, Broadbent, McQueen, & Kaptein, 2011; Patel & Taylor, 2002), treatment control (Searle, Noman, Thompson & Vedkara, 2007) and personal control (Ross, Walker & MacLeod, 2004) have all been linked with medication adherence in a range of conditions. From a theoretical perspective, the CSM would assume that patients who perceive more serious consequences from their illness would be more adherent, as they should want to engage in coping behaviours to reduce the consequences of their illness. This is supported in Ross et al. (2004) and Llewellyn et al. (2003). However, in a study with asthma patients, illness consequences had a negative association with adherence (Horne & Weinman, 2002). This may be because patients who are adherent had better control over their illness and were therefore experiencing fewer symptoms. This highlights a common issue with CSM research; it is often not possible to determine whether the illness perceptions are influencing the behaviour, or if the behaviour is influencing the illness perception, both of which are proposed within the CSM.

In patients with hypertension, reporting more illness-related symptoms was associated with a weaker sense of control over the illness, resulting in lower medication adherence (Chen et al., 2011). That identity was a significant predictor of adherence in an asymptomatic condition like hypertension highlights the importance of understanding how patients perceive their symptoms and shows that perceptions are often inaccurate. Personal control is another perception which varies across studies. Ross et al. (2004) found a negative relationship between personal control and adherence in patients with hypertension, perhaps because people who felt in control had other options for controlling their illness and were less likely to take medication. Conversely, Chen et al. (2011) found a positive relationship between personal control and adherence in another group of patients with hypertension. The authors posit that this inconsistency may be due to differences in sample characteristics,

such as household income or locus of control. These discrepancies could also be due to measurement error or differences in interpretation of items across illnesses.

A recent meta-analysis reviewed the evidence for the relationship between illness perceptions and adherence to a range of self-management behaviours including medication adherence. The combined effects sizes ranged from 0.04 to 0.13, indicating weak relationships (Aujla et al., 2016). This supports the results of a previous meta-analysis which found weak relationships between illness representations and adherence, suggesting that the CSM is not a useful model for predicting medication adherence (Brandes & Mullan, 2014). However, the authors of these reviews combined results from a range of health behaviours (medication, diet, exercise, cholesterol control) and across a range of illnesses. The CSM does not presume that relationships between CSM components will be equal across different illnesses, individuals and coping strategies. In fact, as described above, there is evidence to suggest that the relationships between illness representations and adherence will differ significantly across contexts and conditions. Therefore, combining results across conditions is not an appropriate test of the CSM. Furthermore, these meta-analyses have only investigated illness perceptions which make up one part of the CSM, and should therefore not be used to discredit the model as a whole. Studies in these reviews have also been criticised for using static, generic measures of illness perceptions, which fail to take into account the unique biomedical processes and experiences associated with different illnesses (Phillips et al., 2017). The meta-analyses have also not included more proximal beliefs, such as beliefs about treatment efficacy which may show stronger relationships with adherence (Horne, Weinman, & Hankins, 1999; Philips et al., 2017).

2.4.1.1. Medication beliefs

An extended CSM has since been proposed with the addition of these medication beliefs (Figure 2.3), which are categorised as necessity and concern beliefs (Horne et al., 1999). Necessity beliefs represent the patient's perceived need for the treatment. These beliefs may not be synonymous with the treatment's efficacy, but reflect how necessary the patient feels the medication is for them for their current and future health. Concerns include immediate side effects, long term effects on the body, addiction or dependence, immunity or tolerance and a preference for alternative medicine. Adherence is a potential strategy for coping with an illness threat, and whether someone chooses this strategy is likely to be influenced by how they perceive their medication as well as how they perceive their illness. Whilst non-adherence to a medication might seem irrational from the HCPs perspective, to the patient, it likely reflects a common-sense, rational response based on their illness and treatment beliefs. Researchers have proposed that when making a decision about whether or not to take

a medication, patients weigh up their concerns against how necessary they perceive the medication to be. This is known as the Necessity Concerns Framework (NCF).

The Beliefs about Medicines Questionnaire (BMQ) was developed to provide measurement of medication beliefs (Horne et al., 1999). It consists of four subscales; General-Overuse, General-Harm, Specific-Necessity, Specific-Concerns. The general subscales reflect people's overall views of medications in general, whereas the specific subscales are used to assess beliefs about a specific medication and tap into the NCF. Both necessity beliefs and concerns have been found to be significantly associated with medication adherence (Clatworthy et al., 2009; Morgan et al., 2015; Neame & Hammond, 2005).

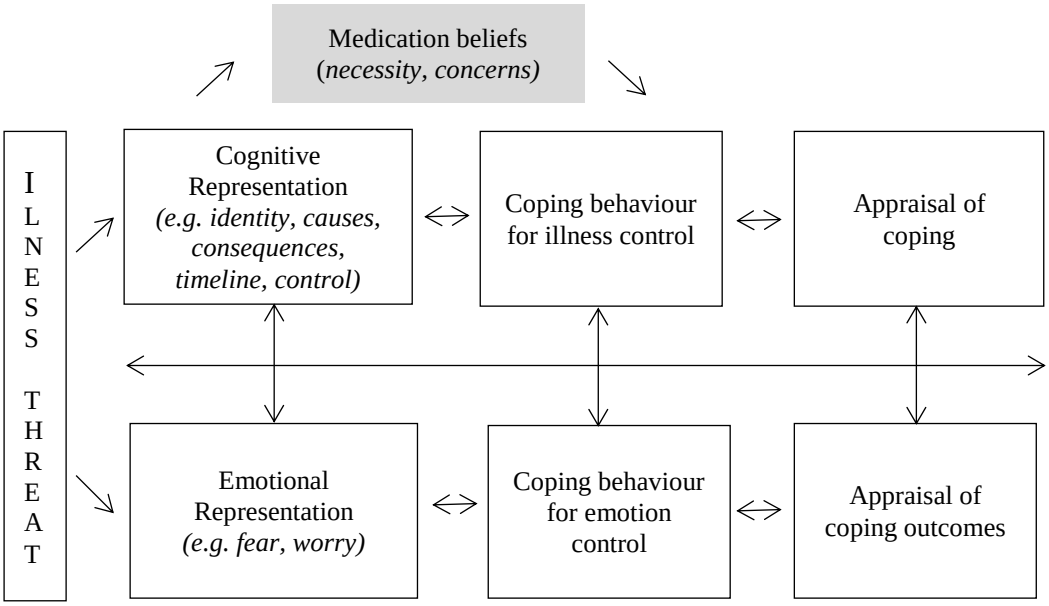

Figure 2.3 Extended Common Sense Model with addition of medication beliefs (Horne & Weinman, 2002)

For example, in a longitudinal study in older adults with multiple illnesses, changes in intentional non-adherence were predicted by changes in necessity beliefs, after controlling for clinical and sociodemographic factors (Schuz et al., 2011). Phatak & Thomas (2006) found that medication beliefs explained 22% of the variation in non-adherence to chronic drug therapy. In a meta-analysis, Horne et al. (2013) found that for every one standard deviation increase in necessity beliefs, the odds of adherence increased by a factor of 1.7 (95% CI=1.6-1.9), and for every one standard deviation increase in concerns, the odds of adherence decreased by 50% (OR=0.5, 95% CI=0.5-0.6). Medication beliefs are more powerful predictors of adherence than clinical or demographic factors (Horne & Weinman, 1999). To further represent the cost-benefit analysis that patients undergo, it is possible to calculate a differential score between necessity and concerns, by subtracting the concerns score from the necessity score. This differential score, which takes into account the weighing

of concerns against perceived need, is a more consistent predictor of non-adherence than necessity or concerns alone (Foot, Caze, Gurjal, & Cottrell, 2016; Horne & Weinman, 1999).

The NCF has also been used to investigate differences between intentional and unintentional non-adherence. Clifford et al. (2008) found that the necessity/concerns differential was predictive of intentional but not unintentional non-adherence in patients with chronic illnesses. However, in another large cross-sectional study across illness groups, unintentional non-adherence was predicted by necessity beliefs (Gadkari & McHorney, 2012). This is likely because people who have high necessity beliefs will place high importance on making sure they do not forget their medication and will set reminders or implement strategies to help them remember. Concern beliefs have also been associated with unintentional non-adherence (Unni & Farris, 2011). The fact that these beliefs are associated with unintentional non-adherence suggests that the behaviour may not be as unconscious as previously thought, and may be more of a motivated forgetting where patient's beliefs about the medication influence how much salience they place on remembering to take it (Lehane & McCarthy, 2007; Unni, 2008; Wroe, 2002).

Researchers have proposed that relationships between illness perceptions and adherence may be mediated through treatment beliefs. In a sample of patients with asthma, the influence of illness perceptions on treatment adherence was found to be largely mediated by necessity beliefs (Horne & Weinman, 2002). Patients who have few asthma consequences and who perceive a short timeline were less likely to believe in the necessity of the preventer treatment and were therefore less adherent. Similarly, Ross et al. (2004) found that higher necessity beliefs were associated with perceptions that the illness would last a long time, stronger consequences and stronger beliefs in the likelihood of cure. Concern beliefs were best predicted by emotional responses, perception of consequences and age. These results support the assumption that medication beliefs are more proximal to adherence than illness beliefs (See Figure 2.3).

Unni & Shiyanbla (2016) conducted a cluster analysis of illness and treatment beliefs in 392 patients with asthma. They found five distinct clusters. The first two clusters resulted in patients being adherent. These clusters were termed "rationally accepting" and "illness stimulated accepting". The other three clusters were associated with non-adherent behaviour and were termed "indifferent", "ambivalent" and "sceptical". Patients who were indifferent had low necessity beliefs, low concerns and low threatening illness representations (e.g. high control, low identity, low emotional representations). Patients who were ambivalent, however, had high necessity beliefs, high concerns and high threatening illness

representations (e.g. high consequences, high timeline beliefs). Finally, patients who were sceptical had low necessity beliefs, high concerns and high threatening illness representations. The differences between these three non-adherent clusters highlight how complex the behaviour of non-adherence is.

2.4.1.2. Research using the CSM in breast cancer patients

The CSM has been used as a framework for investigating a range of outcomes in oncology patients. For example, Thong, Kaptein, Vissers, Vreugdenhil, & van de Poll-Franse (2016) found that increased consequences and emotional representations were associated with increased odds of mortality in colorectal cancer survivors, after controlling for demographic, clinical and lifestyle factors. In BCS, illness perceptions have been associated with physical and mental health (Rozema, Vollnick, & Lechner, 2009), psychological distress (Fischer et al., 2013), fatigue (Corbett, Groake, Walsh, & McGuire, 2016), physical activity (Costanzo, Lugtendorf & Roeder, 2011), quality of life (QOL; Ashley, Marti, Jones, Velikova, & Wright, 2015) and fear of recurrence (Corter et al., 2013). Timmers et al. (2014) assessed adherence to anti-cancer agents, and found optimal adherence was associated with higher treatment control. In a similar study, adherence to capecitabine in cancer patients was associated with a range of illness perceptions (Timmers et al., 2016). However, no research has applied the CSM to medication adherence in BCS.

Whilst no research has applied to the CSM to adherence in BCS, several studies have used the NCF, with mixed results. In a cross-sectional study of 205 BCS taking tamoxifen, lower scores on the necessity scale were associated with increased odds of non-adherence. No effects were found for concerns or for the general subscales of the BMQ (Grunfeld et al., 2005). Arriola et al. (2014) conducted a similar study in the US, showing that necessity beliefs were a significant predictor of HT adherence in a multivariate regression model. Concern beliefs showed univariate associations with adherence but were not significant in the multivariate analysis when controlling for other covariates. However, these studies were all cross-sectional and used relatively small sample sizes. A larger study was conducted with 2351 BCS in the US. Results showed that perceived therapy necessity was associated with adherence, but concerns were not (Stanton, Petrie, & Partridge, 2014). Another three studies found no effects of either necessity or concern beliefs on HT adherence or persistence (Bender et al., 2014; Friese et al., 2013; Walker, Rosenberg, Stanton, Petrie, & Partridge, 2016). However, two of these studies had very high levels of adherence, and the others used non-validated measures of beliefs or adherence. Furthermore, Bender et al. (2014) used pre-therapy measures, where patients may have not yet developed their medication beliefs. Two more recent studies have found significant relationships between medication beliefs and

adherence (Brett et al., 2016; Bright, Petrie, Partridge, & Stanton, 2016). The results of these studies suggest that more research is needed to clarify the relationship between medication beliefs and HT non-adherence.

2.4.2. Theory of Planned Behaviour

The central aim of the TPB is to predict behaviour and understand its causes (Ajzen, 1991). The theory states that intention to perform a behaviour is the most immediate determinant of actual behaviour. Intention is in turn influenced by attitudes, subjective norms and perceived behavioural control (PBC; Figure 2.4). The theory also proposes a direct link between PBC and behaviour. Patients' attitudes towards behaviours are determined by their beliefs about the behaviour and whether the behaviour has a favourable or unfavourable outcome. Subjective norms represent whether the majority of other people would approve or disapprove of the behaviour, or if the patient believes that other people in a similar situation are performing the behaviour. It also takes into consideration how important the patient believes it is to follow the social norms, which is referred to as their motivation to comply. PBC represents the individual's perception of their ability to perform the behaviour. It has been argued that this is a distinct construct to self-efficacy, as self-efficacy focuses more on internal factors whereas PBC also takes into account more general external factors such as time pressures, availability of help or financial constraints (Bandura, 1992). Therefore, PBC can vary across different situations and actions due to the differing internal and external barriers. The relative importance of each TPB component in predicting intention and behaviour also varies across behaviours and situations (Ajzen, 1998). The TPB has its origins in social psychology, and whilst it has been applied to health psychology, it is most often used to explain preventative health behaviours such as smoking cessation, physical activity or alcohol use.

Several studies have found support for the TPB in predicting a range of health behaviours. A meta-analytic review by Armitage & Connor (2001) found that across health behaviours, the average multiple correlation between intention/PBC with behaviour was 0.52 and the average multiple correlation of attitude, subjective norm and PBC with intention was 0.63. Godin & Kok (1996) reviewed the TPB across a range of health behaviours and found the theory could explain 41% of the variance in intention, with attitude and PBC being the most consistent predictors of intention. However, the model has come under significant criticism in recent years. In 2014, Sneihotta, Presseau and Araujo-Soares outlined key issues with the TPB and suggested that it may be time to retire the theory.

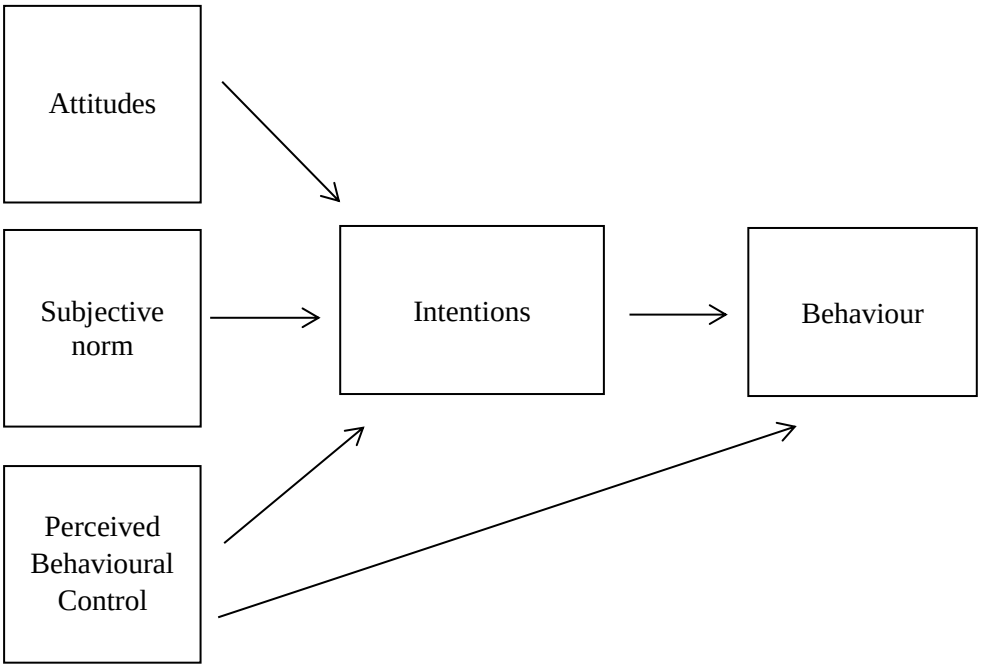

Figure 2.4 Theory of Planned Behaviour

They cited a recent systematic review showing that the TPB only accounted for 19% of the variance in health behaviour (McEachan, Conner, Taylor, & Lawton, 2011). Furthermore, it was found that the theory was less effective at predicting behaviour when studies were longitudinal, if they used objective measures of behaviour and when they used samples other than university students. Although the model proposes that intention is the most immediate determinant of behaviour, research has shown an inability of intentions to predict behaviour, which is known as the intention-behaviour gap. Whilst this gap can often be substantial, Ajzen (2011) has argued that when intention and behaviour are measured within shorter intervals, the intention/behaviour correlation is higher. When there are large gaps between measurement of intentions and behaviour, however, there is a possibility that unforeseen events may prevent someone from carrying out their intentions, resulting in poor correlation between intention and behaviour. This suggests that the TPB may be better able to predict treatment initiation and immediate adherence rather than longer term adherence and persistence.

The theory was also criticised for its focus on rational reasoning, which ignores the role of emotions and unconscious influences on behaviour (Sniehotta et al., 2014). However, Ajzen (2015) argued that Sneihotta's arguments were misguided and were the result of poor understanding of the TPB. He argued that the TPB never assumes that the individual is acting rationally or that their beliefs and attitudes accurately represent reality. Instead, the theory assumes that intention and behaviour are influenced by attitudes, subjective norm and

PBC, but that these factors may be based on information which is incomplete, biased or inaccurate, much like illness perceptions. Another criticism of the TPB is the lack of consideration for how demographic or personal factors might influence behaviour. Finally, Sniehotta et al. (2014) argued that there is a deficit of experimental tests and that the theory does not help with intervention development. Hardeman et al. (2002) conducted a review of 24 studies assessing interventions based on the TPB, concluding that there was insufficient evidence to make assumptions on the usefulness of the theory. However, Trafimow (2014) pointed out that it is very hard to achieve large amounts of behaviour change, and this should therefore not be a specific criticism of the TPB. Implementation intentions, which tie specific behaviours to environmental cues, have shown promise at changing health behaviours by increasing the likelihood that intentions will translate into behaviour (O'Carroll, Chambers, Dennis, Sudlow & Johnston, 2013; Sheeran & Orbell, 2000). Conner (2015) argued that instead of retiring the TPB, we should focus on the contributions it continues to make in the health domain, and the ways in which the theory can be extended.

Despite the criticisms associated with the TPB as a whole, a large amount of research has found it to be a good framework for understanding medication adherence. Bane, Hughes & McElnay (2006) studied medication adherence in 139 hypertensive outpatients. Regression analysis showed that intention and subjective norms explained 41% of the variance in medication adherence. Sivell, Elwyn, Edwards and Manstead (2013) found that intentions to undergo breast surgery were predicted by subjective norms, PBC and attitudes. In a study of 117 South Africans with hypertension or diabetes, Kagee & van der Merwe (2006) found that attitudes, PBC and subjective norms accounted for 47% of the variance in intentions to adhere and 23% of the variance in self-reported adherence. Similar results have been found in medication adherence in organ transplant patients (Chisholm, Williamson, Lance, & Mulloy, 2007), adherence to a gluten free diet (Sainsbury & Mullan, 2011), medication adherence in epilepsy (Lin, Updegraff, & Pakpour, 2016), adherence to HRT (Legare et al., 2003) and mammography uptake (Godin et al., 2001; Rutter, 2000). There are also several benefits to the TPB which highlight its utility for understanding medication adherence. Firstly, the constructs are clearly defined and the relationships between constructs are clearly specified. Secondly, the model comprises few concepts and therefore it is possible to test the full model in smaller sample sizes.

2.4.2.1. Research using the TPB in breast cancer patients

Whilst several studies have found the TPB to be a useful framework for understand breast screening behaviours and intentions (Mason & White, 2008; Rutter, 2000; Tolma, Reininger, Evans, & Ureda, 2006), no research has applied it to medication adherence in BCS. One

study found that attitude, subjective norms and PBC explained 45% of the variance in intentions to exercise in a sample of BCS, and that intentions were a significant predictor of exercise behaviour (Blanchard, Courneya, Rodgers & Mumaghan., 2002). Similarly, Courneya, Friedenreich, Sela, Quinney and Rhodes (2002) found that adherence to an exercise program for cancer survivors was predicted by gender, extraversion, normative beliefs and PBC. However, in both these studies exercise was measured with self-report measures. Objective activity monitors may provide a more accurate assessment of exercise adherence. As of yet no research has used the TPB as a framework for understanding medication adherence in BCS.

2.4.3. Comparison of models

The TPB provides a useful framework for understanding medication adherence; however, it is still only able to account for up to 40% of the variance in intention and behaviour. Likewise, studies show that the CSM is only about to account for up to 27% of the variance in medication adherence (Chen et al., 2011; Horne & Weinman, 2002; Llewelyn et al., 2003). Therefore, focussing solely on one model may provide insufficient explanation of adherence behaviour. There is considerable overlap across most models of health behaviour, but each model brings unique contributions, which may aid with explanation of behaviour. Combining the CSM and the TPB may present greater understanding of why women do not adhere to tamoxifen, as the benefits of one model may overcome the shortcomings of another. Combining these models also has the potential to enhance the effectiveness of interventions to improve adherence (Holmes et al., 2014; Michie et al., 2008). Whilst very little research has been conducted to compare models of health behaviour, several studies have suggested that understanding of health behaviours would be enhanced by use of both the CSM and the TPB (Hunter, Grunfeld, & Ramirez, 2003; Orbell, Hagger, Brown, & Tidy, 2006; Sivell, Edwards, Elwyn, & Manstead, 2011).

The CSM proposes that whether or not someone takes their tamoxifen is dependent on whether the medication taking behaviour makes sense to the patient in light of their common sense beliefs about their illness and treatment. If they perceive their breast cancer to be a serious ongoing condition, they may be more likely to take tamoxifen. If they perceive tamoxifen to be unnecessary for them because they do not perceive any illness threat, they are unlikely to take it. Conversely, the TPB proposes that adherence is motivated by how patients feel about actually taking the medication, whether they perceive any barriers to taking it and whether it is a socially acceptable behaviour. The CSM overlooks the ease or difficulty of actually performing the behaviour and any social norms associated with the behaviour. The TPB covers these aspects but fails to account for how the patient might feel

about their illness or if they have concerns about the medication. There is also no assessment of emotion or emotional responses within the TPB. There is therefore reason to believe that the two theories may complement each other well in the context of medication adherence. Alternatively, by testing and comparing models we may be able to identify superiority of either the CSM/TPB at explaining tamoxifen non-adherence.

Orbell et al. (2006) compared the CSM and the TPB in 660 patients receiving abnormal cervical smear test results. Hierarchal regressions showed that whilst TPB variables could explain 42% of the variance in intentions to attend a follow up clinic, illness perceptions could only explain 4%. Furthermore, when predicting actual clinic attendance, adding CSM variables to the demographic variables did not significantly improve the model fit, but adding TPB variables did. However, whilst the TPB does offer superior prediction of intention and completion of treatment, discriminant function analysis showed that consideration of both models was important in distinguishing between those who attended all of their appointments as scheduled after being prompted, or ceased attending. Whilst the CSM appears to offer little explanation of behaviour in this study, results may not be generalizable to a sample that have already been diagnosed with an illness and already hold representations of the illness. Moreover, this study did not measure treatment beliefs, which may have improved the predictive power of the CSM.

In a similar study, Hunter et al. (2003) compared the CSM and the TPB in the context of help-seeking for breast symptoms. Five hundred women completed a questionnaire assessing CSM and TPB components. Results showed that illness perceptions accounted for 22% of the variance in help-seeking intention. Addition of TPB components significantly improved the model fit and explained a further 7% of variance. Significant predictors were identity, attitude and PBC. The two models provided lower explanation of variance than in the Orbell et al. (2006) study, and in contrast with the previous study, results showed that the CSM explained more variance than the TPB. These discrepancies may be related to the populations studied. In Hunter et al. (2003), women were asked about hypothetical symptoms and behaviour, whereas in Orbell et al. (2006), participants were already faced with a health threat and an associated behaviour to control the health threat. The TPB is therefore much more likely to be relevant in this second population, where participants may have already begun appraising their ability to carry out the behaviour. The healthy women in the breast cancer study are unlikely to have thought about the TPB variables in relation to this hypothetical behaviour. Furthermore, Hunter et al. (2003) did not include emotional representations, which may have enhanced the CSM, and found low reliability for some of the IPQ-R subscales. Nevertheless, both studies show that combining the CSM and the TPB may be useful in understanding health behaviour. Results suggest that participants may

undergo a two stage appraisal process where they evaluate the health threat (CSM), alongside the advantages and disadvantages of the health behaviour (TPB). This two stage process is likely to be relevant in tamoxifen adherence, as beliefs relating to the health threat and the medication efficacy may be equally as relevant as beliefs relating to the patient's ability to take the medication. As described above, researchers have suggested that using multiple models can provide greater understanding of behaviour and is therefore likely to enhance effectiveness of interventions (Corda et al., 2010; Holmes et al., 2014; Michie et al., 2008; Nigg &Jordan, 2005).

2.5. Overview of thesis

The current thesis aims to identify barriers associated with adherence to tamoxifen in BCS. Understanding tamoxifen adherence and identifying modifiable barriers to adherence will aid in the development of interventions to increase adherence rates, which have the potential to improve clinical outcomes. Chapter 3 provides the results of a systematic review which was conducted to examine the pre-existing literature on barriers and facilitators of HT adherence. Both clinical/demographic factors and modifiable psychosocial factors were identified. Chapter 4 presents a qualitative study which was carried out in order to gain understanding of what it was like for women to take tamoxifen, what motivates women to take it, and what factors might be associated with non-adherence or discontinuation. Non-adherence is a complex and multi-faceted behaviour, and researchers have highlighted a need for more qualitative research to help understand why people do not take their medication and to develop interventions to increase adherence (Harrow et al., 2014; Verbrugghe et al., 2013).

Previous research on tamoxifen non-adherence has focussed on clinical and demographic factors and has largely failed to use validated models of health behaviour as a framework for understanding non-adherence. These models help to identify determinants of adherence and provide a blueprint for intervention development. This PhD will use two models of health behaviour as a framework for understanding tamoxifen non-adherence; the CSM and the TPB. In order to measure illness perceptions, a key component of the CSM, there was a need to modify the existing IPQ-R in order to ensure it was relevant and applicable to BCS. The modification and validation of this questionnaire is presented in Chapter 5. Chapter 6 presents a large cross-sectional study carried out to identify factors associated with tamoxifen non-adherence and to test the utility of the CSM and TPB at explaining non-adherence to tamoxifen.

Chapter 7 presents cross-sectional analysis exploring the experience and attribution of menopausal symptoms of women taking tamoxifen. This analysis helps to provide context for what it is like for women to take tamoxifen, and helps to explain why women might become non-adherent. As a limitation with previous work using the CSM and TPB is the lack of prospective data, Chapter 8 provides a longitudinal analysis of predictors of tamoxifen non-adherence. This will identify if the predictors of non-adherence identified in the cross-sectional analysis will also predict later non-adherence. Women in their first year of treatment were followed up at three time points to examine how adherence changes over time and to identify predictors of change over time. As the CSM is a dynamic model which proposes that illness representations and coping styles will be adjusted over time, changes in psychological variables over time were also examined. At the time of writing the thesis, no studies have designed interventions to improve tamoxifen adherence, despite the high prevalence and clinical importance of non-adherence. Chapter 9 describes the development of a self-management intervention for women taking tamoxifen. The intervention was informed by the results of the previous studies to help support women with their tamoxifen treatment, with the aim of improving adherence rates. Feasibility and acceptability of this intervention is described in Chapter 10. Finally, an overall discussion of the thesis is presented in Chapter 11.

3. Systematic Review of barriers and facilitators of hormone therapy adherence and persistence

3.1. Chapter overview

The previous chapter has shown that tamoxifen non-adherence is an issue of significant clinical importance. Therefore, there is a need to understand non-adherence further and to identity factors which may be associated with non-adherence. This current chapter describes a systematic review of barriers and facilitators to Hormone Therapy (HT) adherence and persistence. This review was a vital step in meeting the aims of the PhD and informing the remaining body of research. The aims of the systematic review were to identify factors related to HT adherence or persistence, including clinical or demographic factors as well as modifiable psychosocial factors. The results of this review will help to inform the qualitative study by highlighting any areas where more in-depth investigation may be needed, such as the relationship between side effects and adherence. It will also inform the longitudinal study by identifying which measures have been validated in this population, if there are any gaps in the literature and if there are any promising results which warrant further investigation. The review will also inform the intervention development by highlighting if there are any consistent predictors of non-adherence which should be targeted in the intervention.

3.2. Published paper

This chapter is published in the following article:

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Article title: Barriers and facilitators of adjuvant hormone therapy adherence and persistence in women with breast cancer: a systematic review

Authors: Zoe Moon, Rona Moss-Morris, Myra S Hunter, Sophie Carlisle, Lyndsay D Hughes

Health Psychology Section, Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

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Corresponding author:
Lyndsay D Hughes
Health Psychology Section,
Institute of Psychiatry, Psychology & Neuroscience,
5th Floor Bermondsey Wing, Guy's Hospital,
London SE1 9RT, UK
Email lyndsay.hughes@kcl.ac.uk

Barriers and facilitators of adjuvant hormone therapy adherence and persistence in women with breast cancer: a systematic review

Purpose: Nonadherence to hormone therapy in breast cancer survivors is common and associated with increased risk of mortality. Consistent predictors of nonadherence and nonpersistence are yet to be identified, and little research has examined psychosocial factors that may be amenable to change through intervention. This review aimed to identify predictors of nonadherence and nonpersistence to hormone therapy in breast cancer survivors in order to inform development of an intervention to increase adherence rates.
Methods: Studies published up to April 2016 were identified through MEDLINE, Embase, Web of Science, PsycINFO, CINAHL and gray literature. Studies published in English measuring associations between adherence or persistence and any predictor variables were included. Eligible studies were assessed for methodological quality, data were extracted and a narrative synthesis was conducted.
Results: Sixty-one eligible articles were identified. Most studies focused on clinical and demographic factors with inconsistent results. Some evidence suggested that receiving specialist care and social support were related to increased persistence, younger age and increased number of hospitalizations were associated with nonadherence, and good patient–physician relationship and self-efficacy for taking medication were associated with better adherence. A small amount of evidence suggested that medication beliefs were associated with adherence, but more high-quality research is needed to confirm this.
Conclusion: Some psychosocial variables were associated with better adherence and persistence, but the results are currently tentative. Future high-quality research should be carried out to identify psychosocial determinants of nonadherence or nonpersistence that are modifiable through intervention.
Keywords: breast cancer, adherence, persistence, hormone therapy

Introduction

Breast cancer is the most common cancer in the UK, with 150 women being diagnosed every day.[1] Three quarters of breast cancers contain receptors for estrogen and are known as estrogen receptor positive (ER+). While breast cancer survival rates are increasing, it is still the second most common cause of death from cancer in women.[1] To increase survival rates and reduce the risk of recurrence, many women with ER+ breast cancer are prescribed hormone therapy (HT), such as tamoxifen, or aromatase inhibitors (AIs), which block the effects of estrogen on cancer cells. Five to ten years of HT significantly reduces rates of cancer recurrence and mortality in women with ER+ early breast cancer.[2,3] Despite

significant clinical benefits, many women do not take HT as prescribed, which leads to a significantly increased risk of mortality and recurrence.[4–6]

Adherence to tamoxifen and AIs ranges from 65% to 79% and 72% to 80%, respectively, but falls over the course of treatment to ~50% by the fourth or fifth year.[7–9] Furthermore, half of patients discontinue HT by 5 years,[10,11] suggesting that a significant proportion of patients are not receiving the full clinical benefits of HT. An understanding of the mechanisms behind nonadherence would facilitate development of effective interventions, with a view to improving adherence and ultimately increasing the survival benefits associated with HT. Clinical and demographic factors may be useful as identifiable risk factors but cannot be modified through intervention. Psychosocial factors, however, are typically modifiable and are highly suitable targets for intervention. For example, illness and medication perceptions, such as necessity and concern beliefs, are predictive of adherence in other illnesses[12,13] and have been successfully modified.[14,15]

A previous review of HT adherence and persistence concluded that little was known about the impact of clinical, demographic, or psychological factors and highlighted a need to research modifiable factors.[16] A significant amount of research has been published since 2012, warranting an up-to-date review. In 2015, Cahir et al[17] carried out a systematic review of modifiable determinants of adherence with a view to developing behavioral interventions. Although the review was useful, there were several limitations, which are addressed by the current review. First, the main conclusions were that side effects, the number of prescription medications and the type of practitioner (general practitioner [GP] vs oncologist) influenced HT adherence or persistence. These factors are mostly not suitable for behavior change intervention. A more targeted review of modifiable psychosocial predictors would provide further guidance for the development of an intervention. Second, as gray literature databases and conference abstracts were not included in the search, some key studies are missing from Cahir et al's review. Finally, the authors conducted a meta-analysis, but due to significant heterogeneity, only a very small proportion of studies could be included, limiting the value of the results. For example, although 13 studies investigated the effects of the number of prescription medications, only four studies were eligible for the meta-analysis. Therefore, a narrative synthesis may be more appropriate. Van Liew et al[18] conducted a narrative synthesis concluding that social support, patient-centered interactions, anxiety and medication beliefs were reliably associated with adherence or persistence. However, this review conducted a limited search of only two databases and may have missed some important eligible studies. Furthermore, empirical interest in this area is growing and a considerable number of studies have been published in the 2 years since the previous reviews.

The current review aims to build upon and address limitations in the previous reviews and identify factors related to HT adherence or persistence by:

(1) conducting an updated and broader search to ensure that all relevant articles are identified;

(2) searching gray literature databases to identify unpublished literature;

(3) combining modifiable psychosocial factors with demographic, clinical and health care factors to provide a comprehensive overview of nonadherence and nonpersistence in this population; and

(4) conducting a narrative synthesis as opposed to a meta-analysis, due to the anticipated significant heterogeneity within the included studies.

Methods

Search strategy

The review was conducted in accordance with PRISMA guidelines.[19] The following databases were searched from inception to April 2016: MEDLINE, Embase, Web of Science; PsycINFO and CINAHL. Search terms included a combination of terms related to, 1) breast cancer, 2) nonadherence or nonpersistence, and 3) HT. Specific search terms are listed in Table S1 (Appendix A). Reference lists of included articles were screened, and gray literature databases were searched.

Study selection

Inclusion/exclusion criteria are shown in Table 1. Participants had to be female, >18 years of age and prescribed adjuvant HT for primary breast cancer. Studies had to be conducted in clinical practice, as adherence rates are often higher in clinical trials.[20] After removing duplicates, one author (ZM) screened titles and abstracts and excluded irrelevant articles. Full texts were then screened for inclusion by two authors (ZM and SC) using a predefined screening table, and one disagreement was resolved. Authors of conference abstracts were contacted to identify unpublished articles, and two authors responded with the full-text articles.

Data extraction

Information was extracted on study design, participant characteristics, adherence measurement, outcome measures and study results. Data were extracted by one researcher. Another researcher independently extracted data from 10% of articles, and there were no disagreements.

Quality assessment (QA)

The QA tool was adapted from Pasma et al[21] based on recommendations from Sanderson et al.[22] Studies were assessed on methods for selecting study participants and measuring study variables, appropriate statistical analyses, loss to follow-up and removal of nonpatient-

initiated nonadherence (eg, due to contraindications). Studies scored 1 if they met each criterion and 0 if it was not met or was unclear. The proportion of criteria met was indicated by a percentage, as some criteria were not applicable for all articles. One author (ZM) conducted QA, and another author (SC) verified a random subset of 10% of articles. An additional author (LDH) resolved one discrepancy.

Results

A total of 6,140 articles were identified, and after removing duplicates and screening titles and abstracts, 120 full-text articles were screened. Sixty-one articles were included in the review (Figure 1). There was heterogeneity between studies in terms of outcome measures, type of effect sizes, definitions of adherence and predictor variables. It is, therefore, inappropriate to conduct a meta-analysis.

Characteristics of studies

The majority of studies were conducted in North America (n=34) and Europe (n=17; Table 2). The mean sample size was 3,042 (range 82–26,179), and there were 181,793 unique participants. Two studies included data analyzed from the same sample.[23,24] One study was a follow-up analysis[25] using the same sample as a previous study.[26] All studies were included in the review. Studies were cross-sectional (n=16), retrospective (n=32) and longitudinal (n=13). Average follow-up for retrospective and longitudinal studies was 3.1 years (SD =1.4) and 2.7 years (SD =1.4), respectively. Twelve studies included patients prescribed tamoxifen, seven studies included patients prescribed AIs and 42 studies included patients on either therapy. Studies measured nonadherence (n=25), discontinuation/nonpersistence (n=29), or both (n=6).

Table 1. Inclusion and exclusion criteria for studies in the review

Inclusion criteria	Exclusion criteria
Patients were all female and aged > 18 years	Articles not in the English language or where the full text was not available
Patients had been prescribed adjuvant HT to treat primary breast cancer	Studies including only DCIS or Stage IV patients
Studies had to be conducted in clinical practice	Studies using an intervention to improve adherence
Studies had to present statistical tests of association between HT adherence or persistence and a correlate or predictor.	Studies investigating initiation to HT
	Studies not providing primary data

Abbreviations: DCIS, ductal carcinoma in situ; HT, hormone therapy.

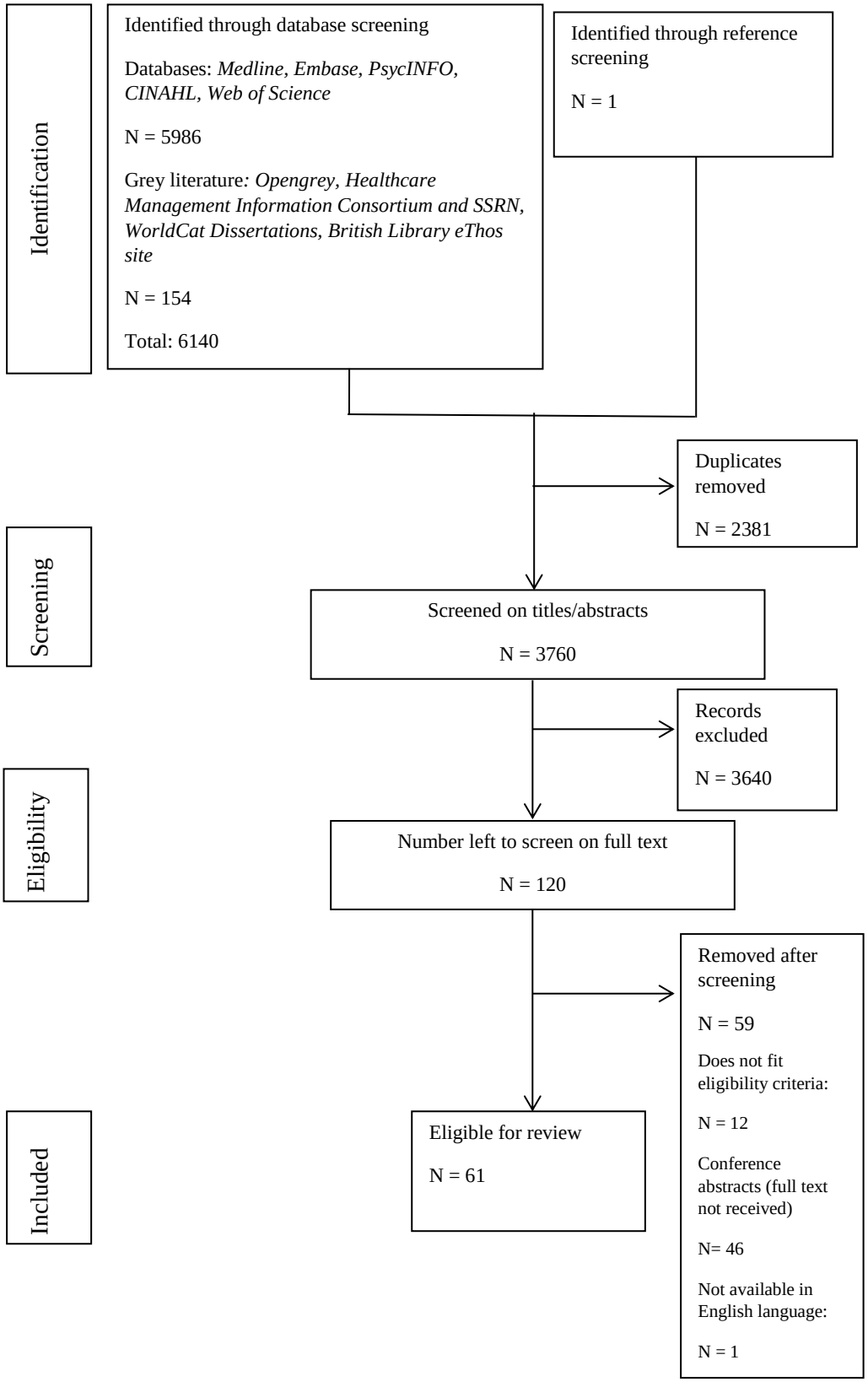

Figure 1. Flow diagram showing results of search strategy.
Abbreviations: HT, Hormone therapy. SSRN, social science research network.

One study measured interruption, defined as a 60-day gap in treatment. Measurements included Medication Event Monitoring System (MEMS; n=2), medical records (n=4), prescription records (n=27), self-report (n=21) and a combination of measures (n=7). Of the studies using self-report, only six studies used validated measures. Nonpersistence was defined as gaps in treatment of 45 days (n=3), 60 days (n=8), 90 days (n=2) and 180 days (n=6).

Risk of bias in included studies

The average quality score was 74%, ranging from 33% to 100% (Table 3). The majority of studies were of moderate quality, but there were eleven low- (<50%) and 22 high-quality (>80%) studies. Several studies using self-report data had a risk of selection bias, and some studies failed to use validated measures (Table 3). Only one-third of the studies removed women from analysis who had had a recurrence or died and, therefore, were no longer prescribed HT.

Summary of results

The percentage of women categorized as adherent ranged from 47% to 97% (mean=74%, SD=13%) and fell from an average of 79% in the first year of treatment to 56% in the fourth or fifth year. Studies using MEMS found the highest adherence rate (93%), followed by self-report (82%) and prescription refill rates (75%). Unintentional nonadherence (e.g., forgetting) was specifically measured in three studies and was found to be more common than intentional nonadherence (mean =31% vs 15%).[27–29] Discontinuation ranged from 9% to 63% (mean =30%, SD =12%). Discontinuation rose from an average of 21% in the first year to 48% in the fifth year. Rates of discontinuation were similar across different measurements (prescription refill, self-report and medical records). In some studies, nonpersistence and nonadherence are clearly separated, making it possible to combine the nonpersistence rates (23%–32%) with the nonadherence rates (9%–28%) to calculate the total proportion of the original sample who are not taking their medication as prescribed. In these studies, this amounts to 33%–50% across 2–4 years of treatment, which highlights the extent of the problem of nonadherence in this population.[8,30–32] However, it is not possible to calculate this from other studies due to measurement and classification issues.

Table 2. Study Characteristics

Study reference	Design (& length of follow up)	N enrolled (N in analysis)	Setting	Age	Other patient characteristics	Medication	Defining non-adherence or non-persistence	Measurement of non-adherence or non-persistence
Aiello Bowles et al. (2012)[51]	Cross-sectional	693 (598)	US	52+	90% Caucasian, Stage I-IIB, post-menopausal	AIs / TAM	Non-persistence (no longer using drug at 5 years)	Self-report
Barron et al. (2007)[54]	Longitudinal (3.5 years)	2816 (2346)	Ireland	35+	Recruited at initiation of therapy	TAM	Non-persistence (180 days no supply)	Prescription refill data
Bender et al. (2014)[40]	Longitudinal (18 months)	91	US	57	88% Caucasian, Stage I-IIIa, ER+, recruited at initiation of therapy	AIs / TAM	Adherence (% MPR)	MEMS
Bhatta et al. (2013)[61]	Cross-sectional	381 (197)	US	< 80	72% Caucasian, Stage I-III ER+	AIs / TAM	Persistence (5 years of therapy)	Self-report
Brito et al. (2014a)[23]	Retrospective (3.3 years)	5861 (5861)	Brazil	58	Stage I-IV	AIs / TAM (64% TAM)	Non-adherence (MPR < 80%)	Prescription refill data
Brito et al. (2014b)[24]	Retrospective (5 years)	5861 (5861)	Brazil	58	Stage I-IV	AIs / TAM (64% TAM)	Non-persistence (60 days no supply)	Prescription refill data
Cheung et al. (2015)[95]	Retrospective (3 years)	5150 (5150)	US	76	88% Caucasian, Medicare beneficiaries	AIs / TAM (22% TAM)	Non-adherence (PDC<80%), non-persistence (60 days no supply)	Prescription refill data
Cluze (2012)[10]	Longitudinal (2 years)	218 (196)	France	18 – 40	Stage I-III, pre-menopausal, HR+, recruited at initiation of therapy	TAM	Interruptions (2+ months no refill)	Prescription refill data
Corter (2013)[46]	Longitudinal (3 months)	125 (120)	NZ	56	Stage I-II, HR+	AIs / TAM (74% TAM)	Adherence (never missed a dose)	Self-report
Danilak & Chambers (2013)[94]	Retrospective (2 years)	346 (346)	Canada	n/s	Stage I-III, HR+	AIs / TAM (81% TAM)	Non-persistence (no longer taking drug)	Prescription refill data

Study reference	Design (& length of follow up)	N enrolled (N in analysis)	Setting	Age	Other patient characteristics	Medication	Defining non-adherence or non-persistence	Measurement of non-adherence or non-persistence
Demissie et al. (2001)[47]	Longitudinal (3 years)	303 (292)	n/s	55+	Stage I - II, 76% ER+, recruited at initiation of therapy	TAM	Non-persistence (no longer taking tamoxifen)	Telephone Interview
Fink et al. (2004)[26]	Longitudinal (2 years)	690 (516)	US	65+	Stage I-IIIa, ER+, recruited at initiation of therapy	TAM	Non-persistence (no longer taking tamoxifen)	Telephone interview
Font et al. (2012)[38]	Retrospective (5 years)	692 (692)	Spain	n/s	Stage I-IIIa, HR+, recruited at initiation of therapy	AIs / TAM	Adherence (MPR = 80-110%)	Various
Friese et al. (2013)[55]	Longitudinal (4 years, cross-sectional analysis for psychological predictors)	3133 (539)	US	59	48% Caucasian, Stage I – III, HR+, recruited at initiation of therapy	HT	Persistence (taken medication in past week)	Self-report
Grunfeld et al. (2005)[66]	Cross-sectional	116 (110)	UK	35 – 65	93% Caucasian	TAM	Adherence (taken drugs every day in past week)	Self-report
Guth et al. (2012)[53]	Retrospective (3 years)	685 (677)	Switzerland	30 – 80	Stage I-III, HR+	AIs / TAM (69% TAM)	Non-persistence (did not complete therapy)	Medical records
Hadji et al. (2013)[43]	Retrospective (3 years)	12,412 (12,412)	Germany	64	Post-menopausal, HR+, recruited at initiation of therapy	AIs / TAM (59% TAM)	Non-persistence (90 days no supply)	Prescription refill data
He et al. (2015)[62]	Retrospective (5 years)	3395 (3395)	Sweden	4% <40, 61% 40-64, 35% >65	Stage I-III,70% post-menopausal, ER+	HT	Non-persistence (180 day gap)	Prescription refill data

Study reference	Design (& length of follow up)	N enrolled (N in analysis)	Setting	Age	Other patient characteristics	Medication	Defining non-adherence or non-persistence	Measurement of non-adherence or non-persistence
Hershman et al. (2010)[8]	Retrospective (4.5 years)	8769 (8769)	US	n/s	76% Caucasian Stage I-III HR+	AIs / TAM	Non-adherence (MPR < 80%) and Non-persistence (180 days no supply)	Prescription refill data
Hershman et al. (2014)[30]	Retrospective (2 years)	4426 (4426)	US	50 +	60% Caucasian Stage I – III	AIs	Non-persistence (gap of 45 days) and adherence (MPR > 80%)	Prescription refill data
Hershman et al. (2015)[31]	Retrospective (2 years)	10,302 (10,302)	US	61	79% Caucasian, Stage I – III	HT	Non-adherence (MPR < 80%), non-persistence (45 days no supply)	Prescription refill data
Hsieh et al. (2015)[39]	Retrospective (4 years)	26,179 (26,179)	Taiwan	52	n/s	AIs / TAM (70% TAM)	Non-adherence (MPR < 80%)	Prescription refill data
Huiart et al. (2012)[70]	Longitudinal (2 years)	288 (246)	France	18-40	Stage I-III, recruited at initiation of therapy	TAM	Non-persistence (90 days no supply)	Prescription refill data
Huiart et al. (2013)[7]	Retrospective (3 years)	382 (233)	France	65+	Stage I-III, post-menopausal, recruited at initiation of therapy	AIs	Non-persistence (90 days no supply)	Prescription refill data
Jacob Arriola et al. (2014)[67]	Cross-sectional	206 (200)	US	59	55% Caucasian, Stage I-IV HR+	AIs / TAM	Adherence (range of scores 0-10)	Self-report (MARS)
Kahn et al. (2007)[48]	Cross-sectional	881 (881)	US	21 – 80	85% Caucasian, Stage I-III, 92% HR+	TAM	Persistence (ongoing use)	Self-report
Karmakar (2013)[69]	Cross-sectional	288 (138)	US	40 – 79	90% Caucasian	AIs	Adherence (range of scores 0 - 8)	Self-report (MMAS)
Kemp et al. (2014)[49]	Retrospective (5 years)	1531 (1531)	Australia	45+	n/s	AIs / TAM (60% TAM)	Non- persistence (180 days no supply)	Prescription refill data

Study reference	Design (& length of follow up)	N enrolled (N in analysis)	Setting	Age	Other patient characteristics	Medication	Defining non-adherence or non-persistence	Measurement of non-adherence or non-persistence
Kimmick et al. (2009)[91]	Retrospective (1 year)	1491 (951)	US	67	59% Caucasian, Stage I-III, HR+/unknown, recruited at initiation of therapy	AIs / TAM (88% TAM)	Adherence (MPR > 80%) and Persistence (no gaps of over 90 days)	Prescription refill data
Kimmick et al. (2015)[27]	Cross-sectional	124 (112)	US	64	91% Caucasian, Post-menopausal, HR+, Stage I – III,	AIs / TAM (18% TAM)	Intentional / unintentional non-adherence (based on scores)	MMAS
Kostev et al. (2013)[45]	Retrospective (3 years)	3620 (3620)	Germany	60	Recruited at initiation of therapy	TAM	Non-persistence (90 days no supply)	Prescription refill data
Kostev et al. (2014)[44]	Retrospective (3 years)	3424 (3424)	Germany	61	n/s	AIs / TAM (61% TAM)	Non-persistence (180 days no supply)	Prescription refill data
Krotneva et al. (2014)[56]	Retrospective (5 years)	3180 (3180)	Canada	70 +	Treated with BCS (no chemo / mastectomy)	AIs / TAM (81% TAM)	Non-persistence (60 days no supply)	Prescription refill data
Kuba (2016)[92]	Retrospective (5 years)	686 (686)	Japan	56	All Asian race, Stage I-III, HR+	HT	Persistence (currently taking medication)	Medical records
Lash et al. (2006)[25]	Longitudinal (5 years)	462 (462)	US	65+	Stage I-IIIA, 87% ER+, recruited at initiation of therapy	TAM	Non-persistence (stopped taking tamoxifen)	Interview questions
Lee et al. (2014)33	Retrospective (2 years)	609 (609)	Seoul	54	Asian women, 89% ER+, no metastasis	AIs	Adherence (no gaps of over 60 days and MPR > 80%)	Prescription refill data
Liu et al. (2013)[50]	Longitudinal (3 years)	921 (669)	US	51	34% Caucasian, Stage I-III, Newly diagnosed	HT	Persistence (hormone use)	Self-report

Study reference	Design (& length of follow up)	N enrolled (N in analysis)	Setting	Age	Other patient characteristics	Medication	Defining non-adherence or non-persistence	Measurement of non-adherence or non-persistence
Livaudais et al. (2012)[96]	Cross-sectional	3575 (3575)	US	69	92% Caucasian, post-menopausal, HR+	Hormone Therapy	Persistence (how long taking the medication)	Self-report
Llarena et al. (2015)[65]	Cross-sectional	515 (515)	US	< 45	71% Caucasian, Stage I – III, HR+, premenopausal,	TAM	Non-persistence (no longer taking medication)	Chart review
Nekhlyudov et al. (2011)[57]	Retrospective (3 years)	2207 (2207)	US	18+	Stage I-III	TAM /AIs	Non-persistence (180 days no supply)	Prescription refill data
Neugut et al. (2011)[32]	Retrospective (1 year)	22160 (22160)	US	67	90% Caucasian, Stage I-III	AIs	Non-adherence (MPR <80%) and Non-persistence (45 days no supply)	Prescription refill data
Owusu et al. (2008)[11]	Longitudinal (5 years)	961 (961)	US	65+	80% Caucasian, Stage I-IIB, ER+ / indeterminate, newly diagnosed	TAM	Non-persistence (60 days no supply)	Medical records
Partridge et al. (2003)[9]	Retrospective (4 years)	2378 (2378)	US	75	83% Caucasian, Stage I-III, recruited at initiation of therapy	TAM	Non-adherence (MPR<80%)	Prescription refill data
Riley et al. (2011)[52]	Retrospective (1 year)	9446 (9446)	US	65+	81% Caucasian, Stage I-III, HR+, entitled to Medicare part D	HT	Non-adherence (MPR<80%)	Prescription refill data
Schmidt (2014)[60]	Retrospective (1 year)	4626 (4626)	Germany	n/s	Stage I-IV post-menopausal HR+	AIs / TAM (40% TAM)	Non-persistence (discontinued)	Medical records
Schover et al. (2014)[42]	Cross-sectional	129 (129)	US	64	81% Caucasian, Stage I – IIA, Node negative	AIs	Adherence (how many days taken it / discontinued)	Self-report
Sedjo & Devine (2011)[34]	Retrospective (1 year)	13593 (13593)	US	<65	Post-menopausal, recruited at initiation of therapy	AIs	Non-adherence (MPR < 80%)	Prescription refill data

Study reference	Design (& length of follow up)	N enrolled (N in analysis)	Setting	Age	Other patient characteristics	Medication	Defining non-adherence or non-persistence	Measurement of non-adherence or non-persistence
Seneviratne et al. (2015)[59]	Retrospective (4 years)	1149 (1149)	New Zealand	60 (24 -99)	80% NZ European, Stage I-III, HR+, newly diagnosed	AIs / TAM (58% AI)	Non-adherence (MPR < 80%)	Prescription refill data
Sheppard et al. (2014)[64]	Longitudinal (3 years)	1062 (1062)	US	65+	89% Caucasian, Stage I-III, ER+, recruited at initiation of therapy	HT	Non-persistence (discontinued)	Self-report
Simon et al. (2014)[93]	Cross-sectional	176 (161)	Canada	57	ER+	AIs / TAM	Adherence (MPR > 80%)	Interview questions
Stanton et al. (2014)[35]	Cross-sectional	2341 (1465)	US	56	Stage I-IV, 94% Caucasian, HR+	AIs / TAM (28% TAM)	Adherence (total MMAS score)	Self-report (MMAS)
Tinari et al. (2015)[28]	Cross-sectional	939 (939)	Italy	62	70% Post-menopausal	AIs / TAM (29% TAM)	Non-adherence (if not taken medication at least 4 times in past month)	Self-report
Trabulsi et al. (2014)[36]	Retrospective (5 years)	4715 (4715)	Canada	65+	Stage I-III, recruited at initiation of therapy	AIs / TAM (95% TAM)	Non-persistence (60 days no supply)	Prescription refill data
Van Herk-Sukel et al. (2010)[63]	Retrospective (5 years)	1451 (1451)	Nether-lands	n/s	Stage I-III 77% HR+ recruited at initiation of therapy	TAM / AIs	Non-persistence (60 day no supply)	Prescription refill data
Walker et al. (2016)[68]	Cross-sectional	82 (82)	US	39 (22-45)	90% Caucasian, Stage 0-IV, diagnosed < 40, HR+,	TAM / AIs (89% TAM)	Non-adherence (score 7+ on MMAS)	MMAS
Wickersham et al. (2013)[41]	Longitudinal (6 months)	198 (198)	Pitts-burgh	59	98% Caucasian, Stage I-III, recruited at initiation of therapy	AIs / TAM (15% TAM)	Non-adherence (MPR < 80%)	MEMS
Wigertz (2012)[37]	Retrospective (3 years)	2071 (1741)	Sweden	n/s	Stage I-III, ER+, recruited at initiation of therapy	AIs / TAM	Adherence (MPR > 80%)	Prescription refill data

Study reference	Design (& length of follow up)	N enrolled (N in analysis)	Setting	Age	Other patient characteristics	Medication	Defining non-adherence or non-persistence	Measurement of non-adherence or non-persistence
Wouters et al. (2014)[29]	Cross-sectional	241 (241)	Nether-lands	57	n/s	AIs / TAM (45% AI)	Adherence (dichotomised as >80% of score distribution)	Self-report (MARS and MMAS)
Wu et al. (2012)[58]	Retrospective (4 years)	612 (331)	US	62	41% Caucasian, Stage I-III, HR+/unknown, recruited at initiation of therapy	AIs / TAM (45% TAM)	Adherence (MPR > 80%)	Prescription refill data
Ziller et al. (2009)[97]	Retrospective (1 year)	100 (89)	Germany	68	Post-menopausal, recruited at initiation of therapy	AIs / TAM (50% TAM)	Adherence (MPR > 80%)	Prescription refill data
Zeeneldin et al. (2012)[98]	Cross-sectional	139 (139)	Egypt	50	Stage I-I, HR+, during Ramadan	AIs / TAM (64% TAM)	Adherence (MPR <80%)	Interview questions

Abbreviations: AIs, aromatase inhibitors; BCS, breast-conserving surgery; ER+, estrogen receptor positive; HR+, hormone receptor positive; HT, hormone therapy; MARS, Medication Adherence Rating Scale; MMS, Medication Monitoring System; MMAS, Morisky Medication Adherence Scale; MPR, medication possession ratio; n/s, not specified; PDC, proportion days covered; TAM, tamoxifen.

Table 3. Quality Assessment

	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	PERCENTAGE
Aiello Bowles et al. (2012)	1	1	1	1	0	1	1	0	n/a	75%
Barron et al. (2007)	0	1	1	1	1	1	1	0	1	78%
Bender et al. (2014)	1	0	1	1	0	1	1	0	0	56%
Bhatta et al. (2013)	1	1	0	0	1	0	1	0	n/a	50%
Brito et al. (2014a)	1	1	1	1	1	1	1	0	0	78%
Brito et al. (2014b)	1	1	1	1	1	1	1	0	1	89%
Cheung et al. (2015)	1	1	1	1	1	1	1	1	1	100%
Cluze et al. (2012)	1	0	1	0	1	1	1	1	1	78%
Corter (2013)	1	1	0	1	1	1	1	0	1	78%
Danilak & Chambers (2013)	1	1	1	1	1	1	1	0	1	89%
Demissie et al.(2001)	1	1	0	1	1	1	1	1	0	78%
Fink et al. (2004)	1	0	1	0	1	1	1	0	1	67%
Font et al. (2012)	1	1	1	1	1	1	1	1	0	89%
Friese et al. (2013)	1	1	0	1	1	1	1	1	1	89%
Grunfeld et al. (2005)	0	0	1	1	0	0	1	0	n/a	38%
Guth et al. (2012)	1	1	0	1	1	1	1	1	1	89%
Hadji et al. (2013)	1	1	1	1	1	1	1	0	0	78%
He et al. (2015)	1	1	1	1	1	1	1	1	1	100%
Hershman et al. (2010)	1	1	1	1	1	1	1	1	1	100%
Hershman et al. (2014)	0	1	1	1	1	1	1	0	0	67%
Hershman et al. (2015)	1	1	1	1	1	1	1	0	1	89%
Hsieh et al. (2015)	1	1	1	1	1	1	1	0	1	89%
Huiart et al. (2012)	1	1	1	1	1	1	1	1	1	100%
Huiart et al. (2013)	1	1	1	1	1	1	1	1	0	89%
Jacob Arriola et al. (2014)	1	0	1	1	1	1	1	1	0	78%
Kahn et al. (2007)	1	0	0	0	1	1	1	1	n/a	63%
Karmakar (2013)	1	0	1	1	0	1	1	1	n/a	75%
Kemp et al. (2014)	1	1	1	1	1	1	1	1	1	100%
Kimmick et al. (2009)	1	1	1	1	1	1	1	0	1	89%
Kimmick et al. (2015)	1	1	1	1	1	1	1	0	1	89%
Kostev et al. (2013)	1	1	0	1	1	1	1	0	0	67%
Kostev et al. (2014)	0	1	0	1	1	1	1	0	0	56%
Krotneva et al. (2014)	0	1	1	1	1	1	1	0	0	66%

	A	B	C	D	E	F	G	H	I	PERCENTAGE
Kuba et al. (2016)	1	1	0	1	0	0	1	0	0	44%
Lash et al. (2006)	1	0	0	0	1	1	1	0	0	44%
Lee et al. (2014)	1	1	1	1	1	1	1	1	1	100%
Liu et al. (2013)	1	0	0	1	1	0	1	0	0	44%
Livaudais et al. (2012)	1	1	0	1	1	1	1	0	n/a	75%
Llarena et al. (2015)	1	1	1	1	1	1	1	1	n/a	100%
Nekhlyudov et al. (2011)	1	1	1	1	1	1	1	0	0	78%
Neugut et al. (2011)	1	1	1	1	1	1	1	1	1	100%
Owusu et al. (2008)	1	1	0	1	1	1	1	1	0	78%
Partridge et al. (2003)	1	1	1	1	1	1	1	1	1	100%
Riley et al. (2011)	1	1	1	1	1	1	1	0	0	78%
Schmidt et al. (2014)	1	1	0	1	1	1	1	0	0	67%
Schover et al. (2014)	0	1	0	1	0	1	0	0	n/a	38%
Sedjo & Devine (2011)	1	1	1	1	1	1	1	0	0	78%
Seneviratne et al. (2015)	1	1	1	1	1	1	1	0	0	78%
Sheppard et al. (2014)	1	1	0	1	1	1	1	1	0	78%
Simon et al. (2014)	1	0	1	1	1	1	1	0	n/a	75%
Stanton et al. (2014)	1	0	1	1	1	1	1	0	n/a	75%
Tinari et al. (2015)	0	1	0	0	1	1	1	0	n/a	50%
Trabulsi et al. (2014)	1	1	1	1	1	1	1	1	0	89%
Van Herk-Sukel et al. (2010)	1	1	1	1	1	1	1	1	1	100%
Walker et al. (2016)	1	0	1	0	0	1	0	1	n/a	50%
Wickersham et al. (2013)	1	0	1	1	1	1	1	0	0	67%
Wigertz et al. (2012)	1	1	1	1	1	1	1	0	1	89%
Wouters et al. (2014)	0	0	1	0	1	1	1	0	n/a	50%
Wu et al. (2012)	1	1	1	1	1	1	1	0	0	78%
Ziller et al. (2009)	1	0	1	1	0	1	0	0	0	44%
Zeeneldin et al. (2012)	1	0	0	1	0	0	1	0	n/a	38%

Notes: A: Are the main features of the study population described? B: Is participation .80% or 60%–80% with no difference between responders and nonresponders? C: Is adherence measured appropriately and clearly described? D: Are other outcome variables measured appropriately? E: Did the analysis control for confounding? F: Are quantitative measures of association presented? G: Was the number of cases in the multivariate analysis at least ten times the number of independent variables in the final model? H: Was physician recommended nonadherence removed? I: Were losses of patients to follow-up taken into account?
Abbreviation: n/a, not applicable.

For example, many studies provide nonadherence figures (using self-report, MEMS and prescription refill) without being explicit as to whether nonpersistent women were removed from analysis or were classed as nonadherent. Others stated that those who discontinued were removed from analysis but have not provided discontinuation rates. Finally, some

authors have classed participants who discontinued treatment as nonadherent and some have allowed participants to be both nonpersistent and nonadherent. Therefore, accurate estimates of nonadherence and nonpersistence rates are currently lacking.

Correlates of adherence and persistence

A large number of variables showed no significant relationship with HT adherence or persistence (Table 4). The remaining factors are discussed later. For the purpose of synthesizing results, variables have been classed as having a positive effect, a negative effect, or no effect on adherence/persistence. A positive/negative effect indicates a statistically significant relationship ($P<0.05$) between adherence or persistence and the predictor variable.

Clinical factors

Adherence

The majority of clinical factors showed no consistent associations with adherence or showed mixed results (eg, tumor size, previous chemotherapy and lymph node status). Switching between HTs was associated with decreased adherence in seven studies[23,28,33–37] and increased adherence in three studies.[8,38,39] The majority of articles did not specify the direction of switching between medications.

Regarding overall side effects, two studies showed a negative relationship with adherence[27,29] and three studies found no significant effects (Table 5). Hot flushes/vasomotor symptoms, incontinence, gastrointestinal symptoms and sex-related symptoms were not associated with adherence, whereas weight concerns were associated with decreased odds of adherence.[40,41] Cognitive, gynecological, musculoskeletal and sleep/fatigue-related symptoms were associated with lower odds of adherence in some studies, but the effects were not consistently found.[40–42]

Persistence

Similar to adherence, the majority of clinical factors were not reliably associated with persistence for the prescribed treatment duration. Three studies found that a codiagnosis of osteoporosis or diabetes was related to increased persistence.[43–45] However, mixed results were found for the effects of comorbidities in general, with the majority of studies finding no significant associations.

Five studies found that experiencing any/severe side effects was associated with decreased odds of persistence,[25,35,46–48] but three studies found no significant effects. Women who experienced menopause-related side effects were up to three times less likely to persist[10,49,50] in three studies but more likely to persist with treatment in two studies.[48,51] Hair thinning was associated with increased odds of persistence, but headaches and loss of appetite showed the

opposite effect.[51] Gynecological symptoms were associated with increased odds of persistence in one study,[51] but another two studies found no significant effects.

Health care factors

Adherence

Consultations with an oncologist or mastologist increased odds of adherence in two studies compared to women without these consultations.[9,23] Experiencing more hospitalizations was associated with lower odds of adherence.[9,23,34,36] Higher monthly prescription costs were associated with decreased odds of adherence in four studies,[30,32,34,52] but two studies found no significant effects.

Persistence

Five studies showed that odds of persistence increased by 21%–66% if treatment was received by an oncologist or a gynecologist as opposed to a general practitioner,[32,43–45,53] while two studies found no significant effect. Five studies found that being prescribed more medications per month was associated with increased odds of persistence;[7,25,26,54,55] however, an additional study showed the opposite effect[32] and three studies found no significant effects. Furthermore, two of the studies showing a positive effect used the same sample at different time points.[25,26]

Table 4. Results from included studies

Predictor variables	Number of studies finding positive/negative effect					
	Adherence			Persistence		
Clinical variables						
Menopausal status (Pre vs. Post)	No effects: 3	Positive: 0	Negative: 0	No effects: 4	Positive: 0	Negative: 1[35]
Laterality	No effects: 1	Positive: 0	Negative: 0	No effects: 2	Positive: 0	Negative: 0
Larger tumour size	No effects: 1	Positive: 1[37]	Negative: 0	No effects: 10	Positive: 0	Negative: 0
More advanced stage	No effects: 12	Positive: 1[36]	Negative: 2[23,33†]	No effects: 12	Positive: 2[64,91]	Negative: 2[24,60]
Positive lymph node status	No effects: 3	Positive: 0	Negative: 1[8]	No effects: 8	Positive: 3[11†,51†,92†]	Negative: 1[26]
Radiotherapy	No effects: 11	Positive: 1[33†]	Negative: 2[23,58†]	No effects :10	Positive: 2[8,56]	Negative: 1[24]
Chemotherapy	No effects: 9	Positive: 3[38,39,58]	Negative: 3[23,33†,93]	No effects: 13	Positive: 5 [8,35†,49,64,94]	Negative: 2[24,26†]
Surgery (yes / no)	No effects: 3	Positive: 1[23]	Negative: 0	No effects: 2	Positive: 1[24]	Negative: 0
Mastectomy (yes / no)	No effects: 0	Positive: 1[34]	Negative: 1[9]	No effects: 0	Positive: 1[49]	Negative: 0
BCS (vs. Mastectomy)	No effects: 10	Positive: 1[33]	Negative: 2[8,39]	No effects: 13	Positive: 0	Negative: 2[8,11]
Positive HR status	No effects: 3	Positive: 0	Negative: 0	No effects: 5	Positive: 3[11,47,48]	Negative: 0
AI (vs. tamoxifen)	No effects: 5	Positive: 4[35,36,38,39]	Negative: 4 [23,58†,67,95]	No effects: 6	Positive: 2[49,51]	Negative: 1[95]
Switching between TAM and AIs (vs. not switching)	No effects: 0	Positive: 3[8,38,39†]	Negative: 7 [23,28,33†,34,35]	No effects: 1	Positive: 2[8,43]	Negative: 2[24†,62]
Presence of comorbidities	No effects: 9	Positive: 3 [9,46,69†]	Negative: 5 [8,27,30,31,34]	No effects: 13	Positive: 2 [50,91]	Negative: 7 [7,8,10,11†,30,62,63]
Diabetes / Osteoporosis	No effects: 0	Positive: 0	Negative: 0	No effects: 0	Positive: 3[43-45]	Negative: 0
Healthcare variables						
Mastologist visits	No effects: 0	Positive: 1[23]	Negative: 0	No effects: 0	Positive: 1[24]	Negative: 0
Oncologist (vs no oncologist)	No effects: 0	Positive: 2[9,23]	Negative: 0	No effects: 3	Positive: 2[24,49†]	Negative: 0
Oncologist vs. Surgeon	No effects: 0	Positive: 0	Negative: 0	No effects: 1	Positive: 0	Negative: 0
Non surgeon as provider	No effects: 0	Positive: 1[36]	Negative: 0	No effects: 0	Positive: 0	Negative: 0
Primary care vs. oncologist / gynaecologist	No effects: 1	Positive: 0	Negative: 1[32]	No effects: 2	Positive: 0	Negative: 5[32,43-45,53†]

Predictor variables	Number of studies finding positive/negative effect					
	Adherence			Persistence		
Oncologist vs. Gynaecologist	No effects: 0	Positive: 0	Negative: 0	No effects: 0	Positive: 0	Negative: 1[60]
More prescription medications	No effects: 8	Positive: 2[33,36]	Negative: 0	No effects: 3	Positive: 5 [7,25,26†,54,55]	Negative: 1[32]
Complementary / Alternative Medicine use	No effects: 0	Positive: 0	Negative: 0	No effects: 0	Positive: 0	Negative: 1[7]
90 day prescription refill period (vs. 30 days)	No effects: 0	Positive: 1[8]	Negative: 0	No effects: 0	Positive: 1[8]	Negative: 0
More Hospitalisations	No effects: 1	Positive: 0	Negative: 3[23,34,36]	No effects: 1	Positive: 0	Negative:3[24,56,57]
Higher monthly costs	No effects: 2	Positive: 0	Negative: 4 [30,32,34,52]	No effects: 3	Positive: 0	Negative: 2[30,32]
Demographic variables						
Family history	No effects: 2	Positive: 1[23†]	Negative: 0	No effects: 2	Positive: 1[24]	Negative: 0
Having children	No effects: 3	Positive: 0	Negative: 0	No effects: 4	Positive: 0	Negative: 0
Secondary or higher education	No effects:13	Positive: 1[23]	Negative: 0	No effects: 15	Positive: 1[24]	Negative: 0
Younger age (<40/50)	No effects: 3	Positive: 1[59]	Negative: 9 [9,23,28,31,33†,34,38,39,58]	No effects: 6	Positive: 0	Negative: 7 [8,24,43,44,54,60,62]
Older age (>65/75)	No effects: 5	Positive: 2[28,60]	Negative: 6 [9,30-33†,59]	No effects: 7	Positive: 1[49†]	Negative: 9 [8,11,30,32,48,54,57,62,63]
Higher mean age (continuous)	No effects: 9	Positive: 3[27†,29,67]	Negative: 1[69†]	No effects: 4	Positive: 1[55]	Negative: 2[36,64]
Race (other vs. Caucasian)	No effects: 8	Positive: 0	Negative: 2[9,27†]	No effects: 7	Positive: 0	Negative: 1[30]
Race (black vs. Caucasian)	No effects: 3	Positive: 0	Negative: 4[8,31,32,52]	No effects: 5	Positive: 0	Negative: 0
Race (Latina vs. Caucasian)	No effects: 0	Positive: 0	Negative: 0	No effects: 1	Positive: 0	Negative: 0
Race (Hispanic vs. Caucasian)	No effects: 5	Positive: 0	Negative: 0	No effects: 4	Positive: 1[11†]	Negative: 0
Race (Asian vs. Caucasian)	No effects: 4	Positive: 0	Negative: 0	No effects: 3	Positive: 1[8]	Negative: 0
Race (Less-acculturated Latina vs. Caucasian)	No effects: 0	Positive: 0	Negative: 0	No effects: 0	Positive: 1[50]	Negative: 0
Maori or Pacific vs. NZ European	No effects: 0	Positive: 0	Negative: 1[59]	No effects: 0	Positive: 0	Negative: 0
With partner / Married	No effects: 9	Positive: 6 [8,23,32,37,52,69†]	Negative: 1[91]	No effects: 7	Positive: 3[8,24,64†]	Negative: 2[65†,91]
Perceived financial status / problems	No effects: 0	Positive: 0	Negative: 1[35]	No effects: 4	Positive: 0	Negative: 0

Predictor variables	Number of studies finding positive/negative effect					
	Adherence			Persistence		
Lower income/net worth/SES	No effects: 9	Positive: 0	Negative: 4 [30,31,68†,69†]	No effects: 7	Positive: 0	Negative: 1[31†]
Smoking	No effects: 0	Positive: 0	Negative: 1[23]	No effects: 1	Positive: 0	Negative: 2[24†,65]
Alcohol	No effects: 0	Positive: 0	Negative: 1[23]	No effects: 1	Positive: 0	Negative: 1[24]
Higher BMI	No effects: 1	Positive: 0	Negative: 0	No effects: 4	Positive: 0	Negative: 0
Psychosocial variables – related to HT treatment and healthcare professionals						
Perceived efficacy of HT	No effects: 1	Positive: 0	Negative: 0	No effects: 0	Positive: 0	Negative: 0
HT concern beliefs	No effects: 6	Positive: 0	Negative: 2[27†,67]	No effects: 0	Positive: 0	Negative: 0
HT necessity beliefs	No effects: 4	Positive: 3[35,66†,67]	Negative: 0	No effects: 0	Positive: 0	Negative: 0
Neutral or negative decisional balance score (beliefs)	No effects: 0	Positive: 0	Negative: 0	No effects: 0	Positive: 0	Negative: 2[25,26]
Coping Appraisal (beliefs about HT efficacy and self-efficacy over costs)	No effects: 0	Positive: 1[69]	Negative: 0	No effects: 0	Positive: 0	Negative: 0
Negative emotions about HT	No effects: 0	Positive: 0	Negative: 2[35,68†]	No effects: 0	Positive: 0	Negative: 1[35]
Positive emotions about HT	No effects: 1	Positive: 1[68†]	Negative: 0	No effects: 0	Positive: 1[35]	Negative: 0
Perceived importance of HT	No effects: 0	Positive: 1[61]	Negative: 0	No effects: 0	Positive: 0	Negative: 0
Adherence Estimator (beliefs about efficacy, value, and cost of HT)	No effects: 0	Positive: 1[42†]	Negative: 0	No effects: 0	Positive: 0	Negative: 0
Symptom attribution	No effects: 1	Positive: 0	Negative: 0	No effects: 0	Positive: 0	Negative: 0
Being involved in decision making / discussed HT with doctor	No effects: 0	Positive: 0	Positive: 0	No effects: 2	Positive: 1[48]	Negative: 0
Not told about side effects	No effects: 0	Positive: 0	Positive: 0	No effects: 0	Positive: 0	Negative: 1[48]
Patient/physician relationship	No effects: 0	Positive: 1[35]	Negative: 0	No effects: 0	Positive:1[35†]	Negative: 0
Value of doctor's opinion	No effects: 0	Positive: 1[61]	Negative: 0	No effects: 0	Positive: 0	Negative: 0
Patient/physician communication	No effects: 0	Positive: 1[67†]	Negative: 0	No effects: 3	Positive: 2[50,64†]	Negative: 0
Received right amount of support	No effects: 0	Positive: 0	Negative: 0	No effects: 0	Positive: 1[48]	Negative: 0
Being able to ask questions	No effects: 0	Positive: 0	Negative: 0	No effects: 0	Positive: 1[10]	Negative: 0
Self-efficacy in patient/physician interaction	No effects: 0	Positive: 1[27†]	Negative: 0	No effects: 0	Positive: 1[50]	Negative: 0
Understanding information	No effects: 1	Positive: 0	Negative: 0	No effects: 0	Positive: 1[10]	Negative: 0
Sufficient information given	No effects: 0	Positive: 0	Negative: 0	No effects: 1	Positive: 1[55†]	Negative: 0

Predictor variables	Number of studies finding positive/negative effect					
	Adherence			Persistence		
Perceived self-efficacy (learning about medication)	No effects: 0	Positive: 1[29]	Negative: 0	No effects: 0	Positive: 0	Negative: 0
Perceived self-efficacy (taking medication)	No effects: 0	Positive: 3[27,29,69]	Negative: 0	No effects: 0	Positive: 0	Negative: 0
Practical problems	No effects: 0	Positive: 0	Negative: 1[29]	No effects: 0	Positive: 0	Negative: 0
Psychosocial variables – related to breast cancer						
Fear of cancer recurrence	No effects: 3	Positive: 0	Negative: 0	No effects: 0	Positive: 2[10,55†]	Negative: 0
High coherence beliefs	No effects: 0	Positive: 1[46]	Negative: 0	No effects: 0	Positive: 0	Negative: 0
Personal control, illness consequences	No effects: 1	Positive: 0	Negative: 0	No effects: 0	Positive: 0	Negative: 0
Treatment control	No effects: 0	Positive: 1[46†]	Negative: 0	No effects: 0	Positive: 0	Negative: 0
Perceived ageism in cancer care	No effects: 0	Positive: 0	Negative: 0	No effects: 0	Positive: 0	Negative:1[64†]
General psychosocial variables						
Quality of life / emotional health	No effects: 2	Positive: 0	Negative: 1[40†]	No effects: 5	Positive: 0	Negative: 0
Optimism	No effects: 0	Positive: 0	Negative: 0	No effects: 0	Positive: 1[64†]	Negative: 0
Fatalism	No effects: 0	Positive: 0	Negative: 0	No effects: 1	Positive: 0	Negative: 0
Anxiety	No effects: 4	Positive: 0	Negative: 1[40†]	No effects: 1	Positive: 0	Negative: 1[49]
Depression	No effects: 3	Positive: 0	Negative: 3[34,40†,41†]	No effects: 5	Positive: 2[43,44]	Negative: 1[35]
Low social support	No effects: 1	Positive: 0	Negative: 0	No effects: 0	Positive: 0	Negative: 3[10,64†,70]
Cognitive impairments	No effects: 0	Positive: 0	Negative: 0	No effects: 2	Positive: 0	Negative: 1[54]
Expressing a desire for future fertility	No effects: 0	Positive: 0	Negative: 0	No effects: 0	Positive: 0	Negative: 1[65]

Note: *The effect was not significant in multivariate analysis or was not tested in multivariate analysis.

Abbreviations: AIs, aromatase inhibitors; BCS, breast-conserving surgery; BMI, body mass index; HR, hormone receptor; HT, hormone therapy; SES, socioeconomic status; TAM, tamoxifen

Three studies found that women who were hospitalized more were less likely to persist with treatment,[24,56,57] but one study found no significant effects. Women who used complementary or alternative therapies had lower odds of persistence.[7]

Demographic factors

Adherence

Nine studies showed lower odds of adherence for women under the age of 40/50 years,[9,23,28,31,33,34,38,39,58] one study found the opposite,[59] and three studies showed no significant effects. Six studies found that older women (>65/75 years) were less likely to be adherent.[9,30–33,59] However, two studies found the opposite effect[28,60] and six studies found no effects. Four studies found that being black was associated with lower odds of adherence than being white,[8,31,32,52] but a further three studies found no significant effects for this relationship.[30,58,61]

Persistence

There was a trend suggesting that younger (<45/50 years) women had lower odds of persistence,[8,24,43,45,54,60,62] but this was not always supported. Nine studies showed that older women were less likely to persist with treatment,[8,11,30,32,48,54,57,62,63] but seven studies found no significant association and one study found the opposite effect.[49]

Psychosocial factors

The following variables showed significant effects on adherence but were only tested in one study: illness coherence[46] and self-efficacy regarding learning about medication[29] (positive effect on adherence) and practical problems associated with medication taking[29] (negative effect on adherence). Optimism showed a positive effect on persistence[64] and expressing a future desire for fertility had a negative effect on persistence.[65]

Adherence

There was some evidence suggesting that medication beliefs were related to adherence. Three studies showed that "necessity beliefs", defined as judgments of personal need for the treatment,[12] were significantly related to increased adherence.[35,66,67] The adherence estimator measures perceived need for medication, concerns and affordability and categorizes people as low, medium and high risk for nonadherence. Women who were high risk were more likely to report being nonadherent.[42] Negative and positive emotions regarding therapy were related to decreased and increased adherence, respectively,[35,68] and perceived importance of therapy was related to increased adherence.[61] Karmakar[69] found that coping appraisal, defined as the effectiveness of taking HT and self-efficacy in ability to take HT, minus the costs of taking HT, was associated with increased odds of adherence.

Table 5. Relationship between side effects and HT adherence / persistence

Variable	Number of studies showing positive / negative effect	
	Adherence	Persistence
Any side effects	2 x negative [27†,29] 3 x no effects	3 x negative [35†,46†,47] 2 x no effects
Severe side effects	0	2 x negative [25,48] 1 x no effects
Overall hormone / menopause related	0	1 x positive [51†] 2 x negative [10,50]
Hot flushes / vasomotor symptoms / sweating	5 x no effects	1 x positive [48] 1 x negative [49] 1 x no effects
Overall sleep / fatigue related	2 x no effects	2 x no effects
Gynaecological symptoms	1 x positive [42†] 2 x negative [40†,41†] 3 x no effects	1 x positive [51†] 2 x no effects
Sex related symptoms	4 x no effects 2 x negative [40†,41†]	2 x no effects
Joint aches and pains / osteoporosis	2 x no effects	2 x no effects
Weight concerns	2 x negative [40†,41] 1 x no effects	1 x no effects
Incontinence /bladder control	3 x no effects	1 x no effects
Hair thinning / loss	0	1 x positive [51†]
Headaches	0	1 x negative [51†]
Loss of appetite	0	1 x negative [51†]
Gastrointestinal symptoms	2 x no effects	0
Cognitive symptoms	2 x negative [40†,41†] 1 x no effects	0

Note. Individual symptoms which were only tested in one study and were not significant are not listed in the table (shortness of breath, eyesight changes, breast sensitivity, fractures/broken bones, retaining water). †indicates that the effect was not significant in multivariate analysis or was not tested in multivariate analysis.

Four studies found no effects of necessity beliefs on adherence.[27,40,46,68] These four studies had small sample sizes and may have lacked power to find a significant effect. However, where effect sizes were given, they were relatively small. Three studies found a positive relationship between perceived self-efficacy for medication taking and adherence.[27,29,69]

Variables relating to patient–physician relationship tended to be associated with adherence. Patient–physician relationship quality,[35] value of doctor's opinion,[61] frequency of physician communication[67] and self-efficacy in patient–physician communication[27] were positively associated with adherence. However, several of these were only tested in univariate analysis and in single studies.

Persistence

Having a neutral or negative decisional balance score, i.e., believing that the benefits of the treatment do not outweigh the harms, was associated with three times lower odds of persistence within the first 2 years of therapy.[26] A 5-year follow-up study supported this relationship but with a smaller effect size.[25] Positive and negative emotions regarding HT were associated with increased/decreased odds of adherence.[35]

Results for patient–physician relationship were mixed. Two studies found that perceptions of better physician communication were associated with increased odds of persistence,[50,64] but three studies found no significant effects. However, one of these effects was nearing significance.[25] Being involved in decisions and discussing HT with a doctor were found to have no significant effects on persistence in two studies and a positive effect in one study.[48] However, being able to ask questions and understanding information,[10] self-efficacy in patient–physician interaction,[50] and receiving the right amount of support[48] were significantly related to increased persistence.

Two studies showed that no longer fearing cancer recurrence was associated with an increased risk of treatment interruption,[10,55] but this did not remain significant in multivariate analysis.[55] Three studies found that women reporting low levels of social support were less likely to persist with treatment.[10,64,70]

Discussion

This article reviewed the evidence for clinical, demographic and psychosocial predictors of HT adherence and persistence to present a holistic view of the evidence base. Empirical interest in this area is growing, and this review builds upon previous reviews by incorporating 27 new studies. One previous review concluded that social support, patient-centered interactions, anxiety and beliefs were related to nonadherence/nonpersistence.[18] While this current review supports some of these findings, new research has questioned whether anxiety is related to nonadherence. Cahir et al[17] found that side effects and follow-up care with a GP (vs oncologist) was negatively associated with persistence and the number of medications was positively associated with persistence. This review supported the previous findings that receiving care from an oncologist was associated with increased persistence but found mixed results for the number of medications and side effects. This review also highlighted new factors, such as younger age and hospitalizations, and moved beyond these findings to identify modifiable factors, such as self-efficacy for medication taking.

Researchers and clinicians often assume that side effects, especially menopausal symptoms, trigger nonadherence.[71,72] Although some studies found a relationship between side effects

and adherence/persistence, the relationship was not always supported.[73] However, studies investigating the effects of hot flushes were low to moderate quality, so further high-quality research is needed. Several studies found that nonadherent or nonpersistent women reported fewer side effects, possibly as a result of not taking the medication. Future research should therefore measure adherence and side effects at several time points to see how the relationship changes across time. Qualitative research has shown that some women would not discontinue HT regardless of its side effects (Moon Z, Moss-Morris R, Hunter M, Hughes L., unpublished data, 2017), which may account for the inconsistent relationship between side effects and adherence.

Being treated by specialists rather than a general practitioner increased persistence. These physicians may provide more specialized and informed care,[43] leading to women being more educated and having positive treatment beliefs, although this was not measured directly. An intervention focusing on knowledge and beliefs may support women who did not receive this from their physician. This is supported by the studies showing that medication beliefs are related to adherence levels.[26,35] Furthermore, several studies showed that variables relating to the patient–physician relationship and physician communication were associated with increased odds of adherence. These results suggest that training primary care physicians to provide more specialized care could improve adherence rates.

Some evidence suggested that women whose insurance data indicated nonadherence or nonpersistence over 1–5 years were more likely to have been hospitalized over the same period. These women may have not taken their medication while in hospital, but as no data were provided for adherence levels during the hospitalization, no strong conclusions can be made. There was relatively consistent evidence from moderate- to high-quality studies, suggesting that younger women had lower odds of adherence and slightly less consistent evidence for a relationship between younger age and nonpersistence. This is in line with previous reviews into adherence in cancer and other illnesses.[74,75] Young women may not take HT due to issues around early menopause or fertility[24] as HT precludes conception. In addition, young women do not adjust as well to a cancer diagnosis, which may affect adherence.[54,76] Results were mixed for the relationship between older age and adherence or persistence.

In terms of modifiable factors, three studies found that women who reported few sources of social support were more likely to discontinue treatment. The importance of social support in maintaining adherence has been highlighted previously,[77,78] but social support was only found to relate to persistence in this review. Discussing the importance of maintaining good social networks and disclosure of cancer status may increase levels of perceived social support. Several studies have shown promise for the effectiveness of social support

interventions.[79,80] Self-efficacy for medication taking, defined as the patient's confidence in their ability to take the medication as prescribed, was associated with increased odds of self-reported adherence.[27] Self-efficacy for medication taking could be modified by teaching patients strategies to remember to take their medication and helping patients to overcome other practical barriers through modeling, goal setting, or confidence building. Similar interventions have been successful at improving self-efficacy for physical activity and dietary behaviors.[81,82]

Patients who held stronger beliefs regarding how efficacious, necessary, important and affordable HT is were more likely to have higher self-reported adherence, as were women who reported more positive emotions around HT. In addition, women who felt that the risks of the treatment outweighed the benefits were three times more likely to discontinue. This relationship between beliefs and adherence is supported by the Necessity Concerns Framework (NCF) and has been demonstrated previously.[83,84] The NCF suggests that adherence is related to holding high perceptions of the necessity of the medication and low concerns. These beliefs are often shown to be more powerful predictors of adherence than clinical or sociodemographic characteristics and have been successfully modified through intervention.[35,83,85] However, the studies investigating beliefs in this review were low- to moderate-quality cross-sectional studies and some used unvalidated measures. In addition, while medication concerns are often found to be predictive of adherence,[83] the majority of studies found nonsignificant results. This suggests that it may be more important to measure how people weigh up their concerns against their necessity beliefs.

The variability between studies may reflect the heterogeneous populations studied. There were discrepancies in geographic location, health care systems and clinical characteristics. Furthermore, while several studies recruited patients at the initiation of treatment, many studies did not specify the stage of treatment. Research has shown that determinants of adherence vary significantly over time.[10] Therefore, future research should try to recruit patients at the same time point, explicitly state participants' stage of treatment and follow them over the duration of the prescription period.

The results from this review suggest that there are no strong predictors of HT adherence or persistence. Reviewing high-quality studies in isolation (n=22) reflected this pattern of inconsistent results. However, the high-quality studies did support the trend of higher rates of discontinuation in older women and lower adherence in black women, suggesting a need to further investigate these relationships. The majority of predictors investigated, such as age, are not amenable to change through intervention. Future research is needed to identify psychosocial factors that have been shown to impact on adherence in other conditions. For example, illness perceptions have been shown to be predictive of adherence in other

illnesses but have not been investigated fully in HT adherence.[12,86] This review identified one study investigating illness perceptions, which found that coherence beliefs, ie, patients' ratings of their understanding of their breast cancer, were the only significant predictors of nonadherence in multivariate analysis.[46] Self-efficacy for taking medication, social support and medication beliefs provide potential targets for intervention. However, higher quality research is needed in order to clarify the relationship between medication beliefs and adherence. Interventions could also focus on training clinicians and general practitioners to improve patient–physician communication.

There are several limitations to this review. It was not possible to conduct a meta-analysis due to significant heterogeneity between studies. This heterogeneity also makes it difficult to compare across studies and make conclusions based on significant predictors of nonadherence. Although a wide search was conducted and attempts were made to identify gray literature, some relevant articles may not have been identified. The conclusions are limited by the methodological quality of the included studies. There was a risk of selection bias in some studies, which means a subset of the population who are potentially more at risk of nonadherence may not be included. Sixteen studies were cross-sectional which limits assumptions about causality. Two studies used MEMS to measure adherence and found very high levels, most likely due to the Hawthorne effect where adherence increases because patients know that they are being monitored.[87] The most common measurement of adherence and persistence was prescription refill, which is known to be the most objective measure.[88] However, this measurement is still flawed, as we do not know if the patient actually took their medication. Several studies used physician ratings, which are likely to grossly overestimate adherence levels.[89] Self-report measures are also susceptible to overreporting due to social desirability. Four studies overcame these limitations somewhat by using validated questionnaires.

There are several reasons that a patient may be recommended by their physician to discontinue treatment, such as recurrence and contraindications. These patients should not be classified in the same way as women who choose to discontinue HT and should be removed from analysis. Around a third of studies attempted to adjust for this by removing women who had a recurrence or who died. Seven studies did not allow patients to switch medications and still be considered persistent, and 13 studies were unclear as to whether they allowed this. Furthermore, only a few studies have clearly distinguished between nonadherence and nonpersistence and provided independent figures for both. Without this information, it is not possible to determine the full medication-taking behavior of these patients and, therefore, the clinical impact. The behaviors and outcomes of completely stopping treatment and occasionally skipping doses are different, so it is important to

understand these as independent with unique predictors. Future research needs to be clear about how nonadherence rates are classified and ideally to provide independent rates for nonadherence and nonpersistence.

Conclusion

Understanding the determinants of nonadherence is essential when designing interventions to improve HT adherence and ensuring that patients realize the full benefits of HT. The main conclusions that can be drawn from this review are that while clinical and demographic factors may be useful in order to identify women at risk of nonadherence, extensive research has not yet identified any consistent predictors. There was some evidence that increased adherence was related to younger age, fewer hospitalizations and better patient–physician relationship, but these relationships were not always supported. Persistence was related to receiving treatment from a specialist. In terms of modifiable factors, there was some evidence to suggest that beliefs about HT, social support and self-efficacy for taking medication were related to adherence and persistence. In order to guide effective interventions to improve HT adherence and persistence, future research should focus on these factors and on identifying additional potentially modifiable factors, which have been shown to be related to adherence in other illnesses.[13] Furthermore, strategies to improve patient–physician relationship and service delivery should be investigated.

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3.3. Update to published paper

The systematic review included papers published up until April 2016. Several studies have been published since this date. The following section will outline these studies and review the findings in relation to the systematic review presented in Section 3.2. Brett et al. (2016) conducted a questionnaire study in 292 Breast Cancer Survivors (BCS) in the UK. Bivariate analyses using chi-squared were conducted and showed that intentional non-adherence, measured with the Medication Adherence Rating Scale (MARS), was associated with more side effects, lower necessity beliefs and higher concerns. Unintentional non-adherence on the other hand was associated with younger age, post-secondary education and paid employment. When these factors were entered together in multivariate analyses, the only significant predictors of non-adherence were presence of side effects (OR=4.38, 95% CI=1.60-12.00) and concerns (OR=1.18, 95% CI=1.03-1.35).

In another large questionnaire study, switching therapies, better patient-oncologist relationship and higher necessity beliefs were all associated with increased adherence, and negative emotions about HT were associated with non-adherence (Bright et al., 2016). Emotions about HT were also examined in a questionnaire study conducted in 523 BCS in the US (Hershman et al., 2016). Results showed that positive attitudes to HT after initiation of treatment were associated with lower odds of non-persistence in the multivariate analysis. Women in the highest income category also had lower odds of non-persistence. However, no relationship was found between persistence and age, race, marital status, education, employment status, tumour stage, lymph node status, comorbidities, chemotherapy, type of HT, decisional balance score or social support. Emotional support was found to be associated with non-adherence in a cross-sectional study of 261 BCS in Ireland (Quinn, Fleming, & O'Sullivan, 2016). Non-adherence was also associated with younger age, being employed and experiencing side effects. All these effects, except age, remained significant in the multivariate analysis. Several other demographic variables such as education and marital status showed no effects on adherence.

Jacob, Hadji and Kostev (2016) reviewed data on 29,245 patients prescribed HT. Results showed that older women (>70 years), women treated in gynaecological practice (vs. general care) and those with more comorbidities had lower odds of non-persistence. Nestoriac et al. (2016) found a correlation between baseline side-effect expectations and adherence rates two years later. Cahir, Barron, Sharp and Bennett (2017) found that of 17 previously identified risk factors, only age, marital status, previous medication use and antidepressant use were associated with completing five years of HT. However, these risk factors did not

discriminate well between women at high or low risk of non-persistence, suggesting there is a need to examine other risk factors. These new studies were of moderate quality, as were the majority of studies in the review. They largely provide support for the findings in the review, although there were several new factors identified in these recent studies which were not supported in the review, such as employment status. Additionally, Brett et al. (2016) provided one of the first comparisons of intentional and unintentional non-adherence, with results suggesting there may be unique predictors associated with each behaviour.

These new studies support the conclusions found in the systematic review that there are few consistent clinical or demographic predictors of HT non-adherence or non-persistence. The results of Jacob et al. (2016) also support the systematic review finding that women treated in gynaecologist or oncologist practices are less likely to discontinue than women treated in general care. As discussed in the review, this is possibly due to the increased knowledge and beliefs found in specialists compared to general practitioners. Alternatively, it could be related to higher levels of trust in the HCP. With regards to potentially modifiable factors, one new study found a significant relationship between adherence and concerns (Brett et al., 2016), but despite this finding, the majority of studies in the review found no effects for this relationship. The lack of an effect in the review may be due to the poor methodological quality of the previous studies; three of the studies which did not find an effect for concerns used non-validated questions to assess concerns (Bhatta et al., 2013; Stanton et al., 2014; Walker et al., 2016), and one study found very high rates of adherence which may have affected the results due to a lack of variance (Bender et al., 2014). Therefore, more high quality research is needed to establish the effect of medication concerns on HT adherence.

The new studies also support the previous conclusions that necessity beliefs, positive attitudes about HT and improved patient/physician relationship are associated with increased adherence and that negative emotions about HT are associated with decreased adherence. However, Hershman et al. (2016) found no effect of decisional balance score or social support on persistence, which contrasts with the effects summarised in the systematic review. The two studies in the systematic review finding multivariate effects of social support on persistence included younger women, for whom social support may be more important (Cluze et al., 2012; Huiart et al., 2012). Moreover, these studies simply measured the number of persons providing social support, whereas Hershman et al. (2016) asked people to rate their perceived level of social support, suggesting that the quantity of support available may be important. Quinn et al. (2016) found that emotional support was related to non-adherence, but social or financial support were not. More research is needed to explore the effects of social support on HT adherence. With regards to decisional balance score, two studies in the review found that patients with a positive decisional balance score were less

likely to discontinue treatment (Fink et al., 2004; Lash et al., 2006), whereas Hershman et al. (2016) found no significant effects for this relationship. Hershman et al. (2016) did not provide information for how they created or measured this variable, which may account for the lack of an effect. Furthermore, they measured decisional balance at baseline, when women may not have had time to develop their beliefs about treatment. The new studies summarised here also add support to the relationship between side effects and adherence, but again, this relationship remains fairly inconsistent, with many studies showing no relationship between side effects and adherence.

The systematic review showed a very variable and inconsistent pattern of results, and the addition of these new studies has not provided much clarity. This variation is likely due to variability in the populations studied and the measurements of both adherence and predictor variables. Study populations varied in terms of the geographic location, the age range of participants, the time since initiation of treatment and the type of HT. All of these factors may contribute to the range of different results seen in the systematic review. In addition to this, adherence and persistence were categorised and measured in a range of different ways, with women being categorised as non-adherent if they missed over 20% of doses in some studies, and if they reported missing only one dose in others. Categorising adherence in this manner is likely to lead to significant variability in the literature. Finally, the quality of the included studies varied considerably. There is a need for higher quality research to attempt to disentangle some of these effects. However, whilst the overall picture was very inconsistent, there were some fairly consistent results which warrant further research, such as medication beliefs and self-efficacy for medication taking.

3.4. Summary

There are few consistent clinical and demographic factors associated with non-adherence. There was some evidence to suggest that adherence was associated with younger age, fewer hospitalisations and better patient/physician relationship and that persistence was associated with receiving care from a specialist. Evidence is mixed for the relationship between side effects and adherence. Few studies have attempted to identity modifiable psychosocial factors, although research interest in this area is increasing. Potentially modifiable factors identified in the literature so far include necessity beliefs, attitudes towards HT, social support and self-efficacy for medication taking. These results support the use of the Common Sense Model (CSM) and Theory of Planned Behaviour (TPB), as most of the factors mentioned above are covered within these models. The systematic review highlighted that the majority of research investigating medication beliefs was of low to moderate quality and therefore high quality research is needed to test these relationships.

More research is also needed to identify additional modifiable factors associated with HT adherence. The vast majority of research conducted so far has failed to use a theoretical framework when investigating determinants of HT non-adherence. Using validated theories provides a structured framework for investigating key determinants of non-adherence, they help with comparison and replicability across studies and they aid with intervention development (Holmes et al., 2014). Therefore, there is a need to conduct more high quality research using theories of health behaviour as a framework.

4. A qualitative study to explore the experiences of breast cancer survivors taking tamoxifen

4.1. Chapter Overview

Several qualitative studies have been carried out recently to explore the experiences of women taking Hormone Therapy (HT). These studies were not included in the systematic review, but they can provide interesting insights into why women may become non-adherent or non-persistent. For example, Cahir et al. (2015a) interviewed 31 women in Ireland and found that women who were adherent and persistent had strong beliefs in the necessity and efficacy of HT. They were also motivated to take HT by their fear of recurrence. A similar study was conducted by Harrow et al. (2014) in Scotland. Analysis of the interviews showed that side effects do not necessarily affect adherence, and that patient's beliefs about HT may be more important. Van Londen et al. (2014b) found that participants who experienced bothersome side effects would weigh up the pros and cons of continuing HT. In the US, Wells et al. (2016) found that adherence to HT was facilitated by a medication taking routine, taking HT with other medications and understanding the consequences of sub-optimal adherence. In this study, side effects were the most commonly mentioned barrier. Finally, Verbrugghe et al. (2015) interviewed 31 Breast Cancer Survivors (BCS) taking HT in Belgium. Results suggested that adherence was related to the balance between the burden of HT (impact of treatment, HT expectations, lack of recognition from healthcare professionals) and capacity to take HT (personal coping resources, social support).

Incorporating the results of the qualitative studies with the conclusions from the systematic review adds further support to the relationship between side effects and adherence (Wells et al., 2016). It also reinforces quantitative findings showing that adherence is related to necessity beliefs, and suggests that adherence may be related more to the interplay between beliefs and side effects than to side effects alone (Cahir et al., 2015a; Harrow et al., 2014; Van Londen et al., 2014). Furthermore, the qualitative studies support the review findings of relationships between self-efficacy for medication taking and adherence (Verbrugghe et al., 2015). Cahir et al. (2015a) identified fear of recurrence as a motivator for adherence; a finding which was not supported by the studies in the systematic review. The qualitative studies also highlight the importance of establishing a medication taking routine and understanding the consequences of non-adherence, factors which were not assessed in the systematic review. Verbrugghe et al. (2015) also highlighted social support as a facilitator to adherence, which supports the conclusions of the systematic review.

The systematic review described in Chapter 3 provides conflicting and inconsistent evidence on predictors of HT adherence or persistence. Most of the relationships between adherence and potential determinants show both positive and negative effects, as well as often showing null effects. Therefore, there is a need to attempt to untangle some of these effects and to examine the lived experience of women taking tamoxifen. Quantitative analysis does not allow for in-depth exploration of some of these factors, such as the relationship between side effects and adherence. In contrast, qualitative analyses are designed to permit open-ended in-depth exploration of peoples' experiences and beliefs. This in-depth analysis provides context for what it is like for women to take tamoxifen, helps with understanding and interpreting some of the quantitative results, and provides information for intervention development. For example, when examining patients' side effects, qualitative analyses allow a broader exploration than quantitative methods, which within the confines of questionnaires cannot examine which side effects are most bothersome, and how these side effects may interact with other variables. This chapter describes a qualitative study with BCS taking tamoxifen.

4.2. Published paper

Article title: Understanding tamoxifen adherence in women with breast cancer: a qualitative study

Authors: Zoe Moon, Rona Moss-Morris, Myra S Hunter, Lyndsay D Hughes

Health Psychology Section, Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

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Keywords: breast cancer; tamoxifen; adherence; medication beliefs

Corresponding author:
Lyndsay D Hughes
Health Psychology Section,
Institute of Psychiatry, Psychology & Neuroscience,
5th Floor Bermondsey Wing, Guy's Hospital,
London SE1 9RT, UK
Email lyndsay.hughes@kcl.ac.uk

Understanding tamoxifen adherence in women with breast cancer: a qualitative study

Objective. Non-adherence to tamoxifen is common in breast cancer survivors and is associated with poor clinical outcomes. This study aimed to understand womens' experiences of taking tamoxifen and to identify factors which may be associated with nonadherence.

Design. A qualitative study using semi-structured interviews.

Methods. Thirty-two breast cancer survivors who had been prescribed tamoxifen took part in interviews conducted face to face or over the telephone. They were transcribed verbatim and analysed using inductive thematic analysiswith elements of grounded theory.

Results. A key theme identified in the data was weighing up costs and benefits of treatment, which resulted in women falling into three groups; tamoxifen is keeping me alive, tamoxifen is not worth the reduced risk of recurrence, or conflicting beliefs about the harms and benefits of treatment. Additional themes were living with risk of recurrence and information & support.

Conclusions. Women who believed that the necessity of tamoxifen outweighed its costs were more likely to be adherent, whereas women who thought that the benefits did not outweigh the side effects were more likely to have discontinued. A third more ambivalent group believed strongly in the importance of treatment, but were struggling with side effects and were often non-adherent. Patients sometimes felt unsupported and discussed a need for more comprehensive information. To increase adherence, future research needs to explore ways to increase beliefs around tamoxifen necessity and how to help women cope with side effects.

Introduction

Breast cancer is the most common cancer among women worldwide with around 1.7 million women diagnosed per year (American Cancer Society, 2015). Over three quarters of these breast cancers are oestrogen receptor positive (ER+), which means that the cancer cells are stimulated by the hormone oestrogen (Harrell et al., 2007). Hormonal therapies (HT) such as tamoxifen are prescribed to female breast cancer survivors in order to reduce the risk of the cancer returning by blocking oestrogen receptors in cancer cells. They are one of the most effective systemic treatments for ER+ positive breast cancer and can almost half the rate of recurrence (Aguilar et al., 2010; Early Breast Cancer Trialists' Collaborative Group, 1998). Recent research has suggested that extending the prescription from five to ten years brings additional clinical benefits (Davies et al., 2013).

Despite this, many women do not take their treatment in accordance with agreed recommendations from their healthcare provider which is termed as non-adherence by the World Health Organisation (Sabate, 2003). Non-adherence can consist of missing or altering doses and/or taking medication "holidays". Non-adherence can be intentional, where the patient makes a deliberate decision not to take the medication as prescribed, unintentional where the patient may forget or not understand the instructions, or a combination of both. Some women also stop treatment completely before the recommended duration of five to ten years, which is known as non-persistence or discontinuation. Both non-adherence and non-persistence are associated with increased risk of breast cancer recurrence and mortality (Barron, Cahir, Sharp, & Bennett, 2013; Hershman et al., 2011). Studies show that by the fifth year of treatment, up to 50% of women have discontinued (Hadji et al., 2013; Owusu et al., 2008).

Adherence rates range over the course of treatment from 41-88% (Murphy, Bartholomew, Carpentier, Bluethmann, & Vernon, 2012) and fall to 50% by the fifth year of treatment (Lee et al., 2014; Partridge, 2003). As non-adherence and non-persistence have similar effects on clinical outcomes, they will both be referred to as "(non)-adherence" when discussing the implication of the research. This is consisten with taxonomies of adherence which define non-persistence as a type of non-adherence (Helmy et al., 2017; Vrijens et al., 2012).

Whilst there has been an attempt to understand the reasons for non-adherence, the majority of research has focussed on clinical and demographic factors, with few consistent predictors identified (Moon et al., 2017a; Murphy, et al., 2012). Improving adherence rates is increasingly important as tamoxifen is now being prescribed for up to ten years instead of five years (Burstein et al., 2014) and is recommended as prophylaxis for women at high risk of breast cancer (NICE, 2013b).

Tamoxifen lowers circulating oestrogen levels and as a result, is associated with a wide range of menopausal side effects. Hot flushes and night sweats are prevalent, occurring in around 80% of women taking tamoxifen (Moon et al., 2016). Other common menopausal side effects include loss of libido, fatigue, vaginal dryness and weight gain, which occur in more than one in ten women. Changes to mood and irritability are reported in 11% - 67% of patients taking tamoxifen (Cella & Fallowfield, 2008; Moon et al., 2016). Tamoxifen is often prescribed to younger, pre-menopausal women, many of whom would not normally be experiencing menopausal symptoms. Non-adherence is often assumed to be driven by these side effects (Demissie, Silliman, & Lash, 2001; Lash, Fox, Westrup, Fink, & Silliman, 2006), however little research has investigated empirically if this is the case. Whilst a small number of qualitative studies have been conducted with breast cancer survivors taking

adjuvant HT, researchers have highlighted a need to conduct more research to understand the complex problem of non-adherence and to develop interventions to increase adherence (Harrow et al., 2014; Verbrugghe, Verhaeghe, Lauwaert, Beeckman, & Van Hecke, 2013). One qualitative study found that women struggled with their understanding of the hormonal nature of tamoxifen (Pellegrini et al., 2010). Another found that many women suffered side effects which reduced their quality of life (QOL), but did not affect adherence (Harrow, et al., 2014), contradicting assumptions that side-effects resulted in non-adherence. However, non-adherent women and those who were premenopausal were under-represented in this study. Another study interviewed women prescribed HT and found that patients were surprised by the wide range of side effects they experienced (Van Londen et al., 2014). They were offered little support with coping with the side effects and had to develop strategies of their own. Verbrugghe et al. (2015) found that expectations regarding tamoxifen, information and social support contributed to HT non-adherence.

This previous research provides insight into the experiences of women prescribed HT, but the studies tended to focus more on the experiences of side effects and less on understanding if and how non-adherence is impacted by side-effects. Furthermore, the majority of previous research has investigated tamoxifen jointly with aromatase inhibitors, which have a significantly different side effect profile (Howell et al., 2005) and are usually prescribed to older, post-menopausal women. More research is needed to understand why women may not adhere to tamoxifen treatment, in order to develop ways to improve adherence. This research aimed to use an inductive qualitative approach to elicit a broad understanding of women's lived experiences of tamoxifen, their motivation to adhere to treatment and identify reasons for non-adherence and non-persistence, in their own words. A better understanding of adherence and non-adherence in this population will provide invaluable knowledge for clinicians, but will also contribute to the design and development of interventions to improve both adherence and quality of life in women taking tamoxifen.

Methods

Participants

The study was approved by the Northampton National Research Ethics Committee (REF 14/EM/1207). Patients were eligible if they had been prescribed tamoxifen for a breast cancer diagnosis, were female, over 18, spoke fluent English, and able to consent for themselves. Participants were recruited from a London breast clinic, local support centres and through online advertisements to ensure a range of menopausal status at diagnosis and treatment durations.

Twenty-one women were approached in clinic and given information about the study. After being given two days to decide if they wanted to participate, these patients were contacted by the researcher. Twelve agreed to participate in the study. The remaining women could not be contacted. Online advertisements were placed on the following websites: Facebook; Macmillan Online Community; Asian Women's Breast Cancer Group; and Cancer Research UK Cancer Chat. Twenty-one women responded to these advertisements, were screened for eligibility and given information about the study. One woman declined to take part and interviews were arranged with the remaining twenty participants. Recruitment continued until data saturation was reached, defined as the point at which no new themes emerged.

Participants were all female, aged from 36 to 77 (mean=55, SD=10.6) (Table 1). Treatment duration ranged from 2 months to 6 years, with a mean duration of 23 months (SD=20). Thirty-eight percent of participants were in their first year of treatment.

Procedure

Clinic patients were told about the research by their clinician, and then introduced to a researcher. The researcher then gave the patient verbal information and an information sheet to take away. Patients were interviewed face to face in a private room or over the telephone. Informed consent was obtained prior to each interview. The interviews were based on a semi-structured interview schedule (Table 2). Questions were open ended and patients were encouraged to bring up issues which felt important to them. Patients were told that the researchers were interested in hearing their experiences regardless of whether they were currently taking their medication. Interviews were audio recorded and transcribed verbatim. Two researchers carried out the interviews.

Data analysis

The interviews were anonymised and pseudonyms applied before being transcribed by a professional transcription company. All transcripts were checked against the recordings for accuracy. The interviews were analysed using thematic analysis, as described by Braun and Clarke (2006), incorporating elements of grounded theory (Glaser & Strauss, 2009). Data-analysis methods were chosen to optimise validity of the data and to develop a coherent picture of the patient's experiences. Inductive thematic analysis is a theoretically flexible approach which allows in-depth exploration of interviewees' experiences and perceptions with data-driven identification of patterns without preconceived assumptions of predefined theories or frameworks (Braun & Clarke, 2014). Elements of grounded theory were used to develop links between themes and provide a richer interpretation of the data.

Table One Clinical and demographic characteristics of participants (n=32)

Pseudonym	Age	Menopausal status (at diagnosis)	Ethnic group	Time on tamoxifen	Adherence	Side effects
Sylvie	52	Post	White	2 years	Discontinued	Severe: HF, mood changes, poor sleep
Mary	49	Pre	White	6 months	Adherent	Mild
Elisabeth	37	Unsure	White	5 months	Adherent	Mild / moderate
Arlene	62	Post	White	2 years	Adherent	Moderate / Severe
Lisa	55	Peri	White	3 months	Adherent	Moderate
Holly	51	Peri	White	4 months	Adherent	None
Emma	45	Pre	White	1 year, 2 months	Adherent	Mild
Lauren	62	Post	White	18 months	Adherent	Mild / Moderate
Dominique	45	Unsure	Black British	3 years	Adherent	Mild
Joanna	46	Unsure	Black British	1 year, 2 months	Adherent	Mild
Barbara	64	Post	White	1 year	Non-adherent	Mild / moderate
Vanessa	63	Post	White	2 years	Adherent	Mild
Kate	52	Pre	White	14 months	Non-adherent	Moderate
Lorena	58	Post	White	1 year	Discontinued (due to blood clots)	Moderate / Severe
Bonnie	61	Peri	White	4 years 8 months	Discontinued	Severe
Tania	54	Peri	British Indian	1 year, 6 months	Adherent	Moderate
Claudia	60	Post	White	1 year	Adherent	Mild
Rosalind	44	Unsure	Mixed Black / British	7 months	Adherent	Mild
Anita	50	Peri	White	2 years	Discontinued	Severe
Marcia	54	Unsure	White	2 months	Adherent	None
Celia	67	Post	White	7 months	Non-adherent	Moderate / Severe
Katie	56	Post	White	4 months	Adherent	Mild / moderate
Hayleigh	36	Pre	White	4 years	Discontinued (for fertility reasons)	None
Jenny	62	Unsure	Black British	1 year	Adherent	Severe
Julie	61	Post	White	6 years	Adherent	None
Ellen	50	Pre	White	2 years	Adherent	None
Miriam	41	Post	Asian / Asian British	5 years	Non-adherent	Moderate / Severe
Michelle	77	Post	White	2 years (then switched)	Adherent	Moderate / Severe

Pseudonym	Age	Menopausal status (at diagnosis)	Ethnic group	Time on tamoxifen	Adherence	Side effects
Shannon	55	Post	Asian / Asian British	5 years	Adherent	Mild
Frances	77	Post	White	2 years, 2 months	Adherent	None
Anna	60	Post	White	2 years	Adherent	None
Lucy	53	Post	Black British	5 years	Adherent	Mild

Table 2 Interview schedule

Interview Questions	Prompts
General Questions	
How long have you been taking tamoxifen for?	
Do you know which brand you were taking?	
When were you diagnosed with breast cancer?	
Experiences of taking tamoxifen	Side effects? How do you cope with side effects?
Tell me about the experience of taking tamoxifen?	Family life?
Has anything changed over time?	Work life?
What would you change about tamoxifen?	Social life?
Adherence	How / when do you take it?
Tell me about the practical side of taking tamoxifen?	How do you remember to take it?
	How often do you take it?
Knowledge about tamoxifen	
What is your understanding of why you are taking tamoxifen?	Prior beliefs / expectations
	Treatment benefits
How long will you keep taking tamoxifen?	Concerns
Prescription process	
Tell me about how you were prescribed tamoxifen?	Who / when?
	What information were you given?
	Relationship with this person?
Overall	
Do you have anything else to add?	
Do you have any tips for other women prescribed tamoxifen?	

After familiarisation with the data, one author generated initial codes, working systematically though the data set. Codes were based on language used by the participants and were applied to each new unit of meaning. Codes were organised into potential themes using thematic maps and tables following discussions with all authors. Themes were internally consistent, coherent and distinctive and were mapped onto the study aims. Following grounded theory, patterns and links between themes were developed in order to move beyond a purely descriptive analysis and to generate a theory within which to understand the data. Codes and themes were discussed within the research team and were modified until a coherent pattern of themes was identified. Transcripts were re-read to

ensure the analysis was grounded in the data, that all items had been given equal attention and to ensure no data had been missed. Analysis was iterative and involved constant comparison; a technique key to both thematic analysis and grounded theory which involves data, codes and themes being constantly compared.

Characterising patients as adherent

For the purpose of analysis, women were categorised as adherent or non-adherent (Table 1) based on information given in the interviews, after being explicitly asked about their medication taking behaviour. Women were considered adherent if they spoke about taking all or nearly all of their medication and non-adherent if they regularly skipped or halved the medication, or took treatment breaks. A few women self-reported having discontinued treatment. Women spoke consistently and explicitly about their medication taking behaviour, specifying if they forgot or skipped doses, which facilitated categorisation. For example, non-adherent women spoke about halving doses (e.g. "*So I've had breaks off it and then I'd go on…because you're meant to take twenty milligrams a day. I'd do half doses like ten milligrams instead.")* whereas adherent women spoke about never missing doses (e.g. *"I never forget to take it. If I do, everybody says have you taken your tablet, have you taken your tablet?").* Two researchers independently classified women and there was 100% concordance between ratings. Two researchers also listed side effects experienced and classified women as experiencing mild, moderate or severe side effects based on their discussion of the impact of the side effects on their QOL. Agreement was 97% for the rating of severity and 89% for the list of side effects experienced. All discrepancies were resolved after discussion.

Results

Thirty two women were interviewed. Interviews lasted on average 44 minutes (range 16-81). Twenty-three women were classed as adherent, four were non-adherent and five had discontinued. Two of the women discontinued on their doctors' recommendations; one due to blood clots and one so that she could conceive.

Figure 1 shows the themes and subthemes identified in the data. A key theme for all women was the process of *weighing up costs and benefits of treatment,* which first consisted of *moving from initial acceptance of treatment,* and then resulted in women largely falling into one of three groups; *tamoxifen is keeping me alive; tamoxifen is not worth the reduced risk of recurrence;* or *conflicting beliefs around the harms and benefits of treatment*. Additional themes were *living with increased risk of recurrence* and *information & support,* both of

which contributed to women's beliefs about treatment and how they weighed these beliefs up. Each of these themes and corresponding subthemes will be discussed in turn.

Weighing up costs and benefits of treatment

Moving from initial acceptance of treatment. When the women were first prescribed tamoxifen, they are happy to follow whatever treatment their healthcare professional (HCP) recommended.

> *"It wasn't a choice at all. I mean they're professionals so I just listened to what they said."* (Barbara, 64, non-adherent)

However, over time, some women begin to question these initial beliefs and weigh them up against what it is actually like to take tamoxifen. This resulted in women falling into one of three groups; those who held beliefs that tamoxifen was keeping them alive; those who felt that the benefits of tamoxifen were not worth the reduced QOL and those who had conflicting beliefs around the harms and benefits.

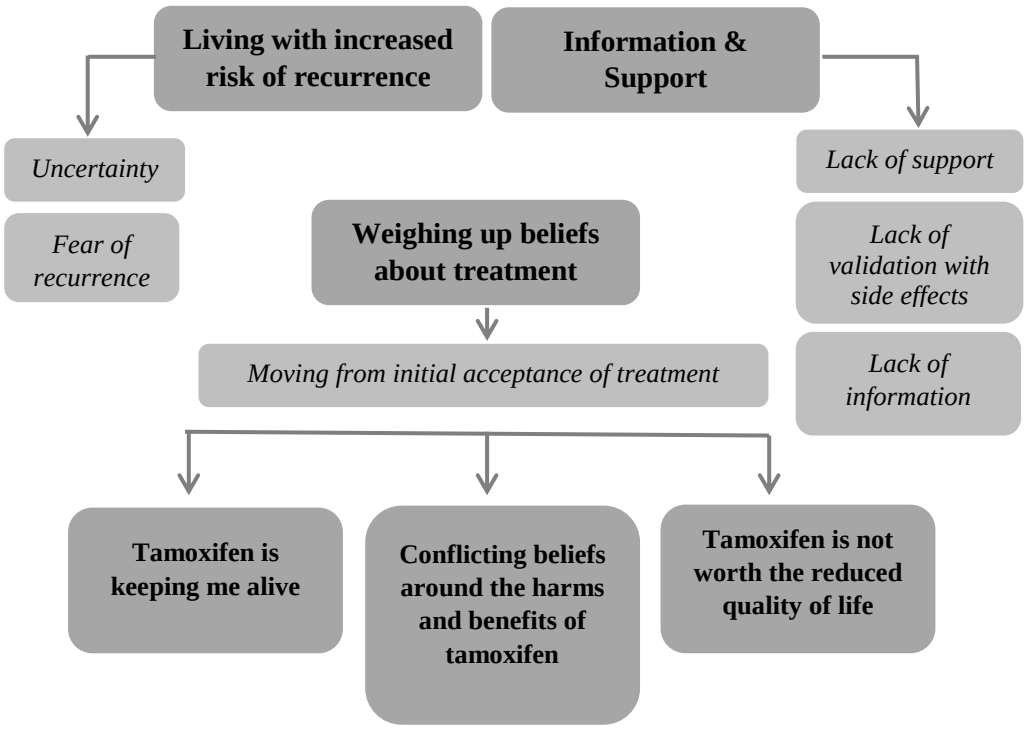

Figure 1. Themes and subthemes identified in the data. Themes are represented by bold text and subthemes by italic text.

Tamoxifen is keeping me alive

Many patients held very strong beliefs regarding the necessity of taking tamoxifen. They felt it was incredibly important to take it every day. Whilst some patients spoke about wanting to avoid going through cancer treatment again, others were more motivated by a fear of death. Some women were also driven specifically by a desire to stay alive for their children.

> *"Well since the option is keep taking it or be dead, it's not much of a choice for me."* (Vanessa, 63, adherent)

Some participants were less certain about the efficacy of tamoxifen, but they still felt it was necessary for them to keep taking it.

> *"Whether like you say with me it would have come back, I just don't know. I'd rather take it than not."* (Ellen, 50, adherent)

As well as necessity beliefs, some women held strong beliefs regarding the control tamoxifen gave them over their risk of recurrence. They liked the fact that tamoxifen was a preventive measure and that it made them feel that they were actively doing something to prevent the cancer returning.

> *"[taking tamoxifen] makes me feel better as well, because I feel like I am doing something actively to prevent it."* (Joanna, 46, adherent)

For some women these control beliefs were so strong that they were concerned about what would happen when their prescription ended.

> *"In one way I was quite looking forward to stopping, but then as it got nearer, I thought, ooh, it's like a safety blanket being taken away isn't it?"* (Julie, 61, adherent)

Most women with strong necessity and control beliefs felt that they far outweighed any concerns they had. They were willing to experience some side effects if it meant they could stay alive and stop the cancer coming back.

> *"Taking tamoxifen just kind of pales into insignificance and it seems like a very small price to pay for not getting breast cancer again."* (Katie, 56, adherent)

The majority of these women were experiencing no side effects or mild side effects. However, some did have side effects which impacted on their QOL, including anxiety, forgetfulness, reduced libido and hot flushes. Despite this, they were willing to keep taking tamoxifen as their beliefs around the necessity of tamoxifen and their desire to stay alive was so strong.

"I never stopped taking it because I thought the nausea and things like that, come on its keeping you alive so stop moaning." (Michelle, 77, adherent)

In order to help them cope with the side effects, many of these women developed coping strategies, such as meditating, removing layers of clothing and exercising. Whilst the majority of women who were adherent had positive views around tamoxifen and were happy to keep taking the medication, one woman disconfirmed this by having negative emotions and beliefs about tamoxifen, yet continuing to take it. She felt that tamoxifen was a reminder of the fact that despite finishing her primary treatment, she still cannot get on with her life.

"I absolutely hate taking this tablet. It's a very powerful drug. It's not just the side effects. It's a reminder of what I had." (Lauren, 62, adherent)

Despite this strong dislike of taking tamoxifen, this patient's necessity beliefs and fear of recurrence were strong and she therefore made sure she took tamoxifen every day.

"I'd be too frightened to be honest not to take it." (Lauren, 62, adherent)

Taking tamoxifen is not worth the reduced quality of life

Whilst some patients had strong necessity beliefs which outweighed their side effects, others felt that the benefits of taking tamoxifen were outweighed by the severe side effects they were experiencing, which led them to discontinue treatment.

"I just couldn't survive anymore taking it. My side effects were so bad I couldn't work…When I stopped and realised the difference, there was no way I was going back on it." (Bonnie, 61, discontinued)

Patients talked about not having enough energy to participate in their lives. They could not maintain relationships with family members and withdrew from social activities. Due to side effects like severe fatigue and depression, tamoxifen had a huge impact on their sense of self, causing them to feel like completely different people.

"When I was on tamoxifen, I was basically stuck in bed or sitting on the sofa feeling very sorry for myself. Just totally different person completely." (Anita, 52, discontinued)

Two women also experienced severe depression and suicidal thoughts. Depression was attributed more to the overall impact of the side effects, which mainly included fatigue, insomnia and muscle cramps, than directly to tamoxifen.

"I can't say that tamoxifen in itself was affecting my moods, but the repercussions of how it [the side effects] affected my life, again it's hard to unpick which was

having the most effect; was it the drug itself or was it just the repercussions of taking it?" (Bonnie, 61, discontinued)

One woman had a strong perception that tamoxifen was causing her to feel suicidal and she felt that this was the tipping point for her to discontinue.

"I felt so low, was having suicidal thoughts, really didn't feel like myself at all, I was in so much pain and that I'd made the decision that I was going to come off tamoxifen." (Anita, 52, discontinued)

These patients received little support from their healthcare teams in how to deal with the side effects, which exacerbated the impact on their lives. HCPs failed to acknowledge that the symptoms they were experiencing were related to tamoxifen and therefore did not offer any assistance.

"I actually was made to feel as if I was having like a mental breakdown...I don't feel as if I was supported properly." (Anita, 52, discontinued)

These women still felt that tamoxifen was an effective treatment for reducing a risk of recurrence, but they no longer felt that the benefits of treatment were worth the side effects and the impact on their QOL. Participants were confident that they had made the right decision and were willing to risk the chance of a recurrence or death in order to improve their immediate QOL.

"I thought actually I would rather be myself for however long that is, rather than be miserable for a longer period, and depending on what… whether the recurrence might occur or not I just thought well I'll take that chance." (Sylvie, 52, discontinued)

Conflicting beliefs around the harms and benefits of tamoxifen

Other patients had conflicting beliefs around the harms and benefits of tamoxifen. They were in turmoil trying to weigh up these beliefs, and to select a behavioural outcome to avoid cognitive dissonance. Many of these women made the decision to skip or halve doses of tamoxifen.

"I've got to the stage where sometimes I'll just give it a miss…I just get so fed up of taking it, I just want to give myself a break." (Miriam, 41, non-adherent)

These patients were struggling to cope with side effects such as fatigue, joint pain, hot flushes and weight gain, which were having a severe impact on their QOL.

> *"It [tamoxifen] is horrible. It really is the most revolting tablet I've ever had to take."* (Kate, 52, non-adherent)

As well as struggling to cope with side effects, patients also had concerns about the increased risk of cancer elsewhere.

> *"I worry more, not about the recurrence, but occurrence in a different part of my body due to this drug that I'm taking."* (Miriam, 41, non-adherent)

In addition to this, women struggled with negative emotions around tamoxifen. For example, some women saw tamoxifen as a reminder of having had cancer, others had negative feelings relating to the impact of cancer treatment on their fertility and some had strong negative feelings about tamoxifen due to their experience of side effects. These negative emotions caused women to attribute a lot of their symptoms to tamoxifen.

> *"It is a hard drug to take because of everything it does. You think tamoxifen's done that, and I do blame it for a lot of things."* (Kate, 52, non-adherent)

Despite these side effects, women wanted to keep taking tamoxifen to reduce their risk of recurrence.

> *"If it was for anything else other than the cancer I would have stopped it, there's no questions, but because of the cancer is such a big thing, you know the possible return of it, that's the only reason I'm struggling with it"* (Celia, 67, non-adherent)

However they were equally as concerned about the side effects and their reduced QOL.

> *"But it's like you're damned if you do and you're damned if you don't. It's that worry if you don't take it, oh god, if they find something again then I think it's because I didn't take the tamoxifen. But on the other hand it's living with all these side effects on it."* (Kate, 52, non-adherent)

Modifying their dosage allows the patient to feel like they are doing something to prevent the risk of cancer returning, but also allows them to exert some control over side effects. However, some patients felt guilty when they missed doses and ultimately resumed treatment if the guilt was too much, or if the fear of recurrence became too strong.

> *"When I don't take it I think oh, god, I should be taking it. I just feel so guilty when I don't take it, but I do feel better when I'm not on it."* (Kate, 52, non-adherent)

Information & support

Lack of information. Some patients felt that they were not always given enough information when prescribed tamoxifen. They had to do their own research on what to expect. Some had very basic knowledge around what tamoxifen was or why they were taking it.

> *"I didn't know anything about it. Really no one's sort of explained what it is. They just said tamoxifen will help stopping recurrence."* (Arlene, 62, adherent)

How informed women feel about tamoxifen is likely to influence how necessary or important they feel it is, which feeds in directly to the previous theme of *weighing up beliefs about treatment*. Additionally, women felt that if they had been told about what side effects to expect they would have been more prepared, which could then improve their management and experience of side effects, potentially reducing the numbers of women who discontinue treatment.

Lack of support. Many women did not feel that they received the support they needed from their HCPs in dealing with the side effects. They would have liked to have been warned about how bad they could be and given emotional support in dealing with them. This is also linked to the previous theme of *weighing beliefs about treatment*, as this support may have helped women who were struggling with side effects, potentially leading them not to discontinue treatment or skip doses.

> *"I think there should be more help, psychologically, with side effects of tamoxifen. I think people ought to be warned."* (Kate, 52, non-adherent)

Some patients went back to their breast clinic or GP for help with their side effects, but were not offered any practical coping strategies for how to reduce the impact of the side effects on their QOL. Patients also wanted more long term monitoring and support whilst they were taking tamoxifen.

> *"I would like there to be more help for people who get this extreme fatigue, whether it's from the radiotherapy or tamoxifen."* (Celia, 67, non-adherent)

Lack of validation with side effects. Some HCPs dismissed or belittled the side effects women were experiencing. Patients were told that their symptoms were not associated with tamoxifen, which left them feeling invalidated and frustrated.

> *"This is the one thing that I do find a lot of women struggling most with, that they feel so…they're just not listened to. They're not being validated in what they're experiencing." (*Bonnie, 61, discontinued)

Furthermore, some patients also felt that their families did not fully appreciate the extent of their side effects and thought the effects of tamoxifen were just linked to previous breast cancer.

> *"I really do think my family thought that I had fallen into a depression and everything just because of the cancer. I think they thought that I thought I was going to die or I just was full of doom and gloom. But it was just out of my control really."* (Anita, 52, discontinued)

Living with increased risk of recurrence

Fear of recurrence. Whilst most women did not identify as still having cancer, nearly all spoke about living in fear of cancer returning. They did not let this fear impact on their daily life, but said it would always be at the back of their mind. Some were not able to relax and were concerned that any little problem might be a sign of cancer.

> *"I find it very difficult to be honest…I think the thing is anything that you find that you feel that is not right in your body then you start thinking 'I wonder if it's something serious'."* (Arlene, 62, adherent)

This fear of recurrence relates to how necessary women feel that tamoxifen is for them, which then plays a key role in whether or not they adhere to treatment. Women who fell into the *tamoxifen is keeping me alive* group spoke about being motivated by avoiding a recurrence. Women who felt that *tamoxifen was not worth the reduced QOL* were less concerned about a recurrence then they were by their side effects. Most women said that they tried to block out this fear and not think about it. Some cited taking tamoxifen as a way to help them control it. Others talked about making changes to their lifestyle to try and be healthier. A few women felt that there was nothing they could do to control the risk of recurrence.

> *"That would be my biggest fear is, it's not, I suppose if it's going to come back it's possibly when, but I can't live my life like that. So I kind of like have to block it and just continue as much as I can."* (Elisabeth, 37, adherent)

Uncertainty about recurrence. Participants reflected on the uncertainty of cancer regarding why it comes back or whether it will come back. They said this uncertainty and fear was hard to deal with.

> *"Someone said to me it's like having a sword dangling above your head, and it is. You just feel like tomorrow you don't know what's going to happen. It's always there in the back of your mind."* (Kate, 52, non-adherent)

For women who were trying to decide whether or not to take tamoxifen, this uncertainty made it harder for them to make a decision.

> *"I can never know what the right answer is, because I don't know whether the cancer will come back. I can't know until it happens."* (Celia, 67, non-adherent)

Women who had discontinued tamoxifen were happy in their decision because they said they wouldn't be able to guarantee that they wouldn't have a recurrence of cancer even if they were taking tamoxifen.

> *"I'll have to deal with that if it happens, and the thing is you've no idea, you have no way of knowing if it would've happened anyway. I'm happy enough*" (Bonnie, 61, discontinued)

Discussion

These results provide insight into the experiences of patients who initiated tamoxifen. Initially, women in this study were happy to take tamoxifen and did not question the doctor's decision. Over time, however, they weighed up the benefits of taking tamoxifen against the harms, leading to some patients becoming non-adherent or non-persistent. Women who felt that the necessity of taking tamoxifen far outweighed the side-effects were more likely to be adherent. Women who felt that the side effects were not worth the benefits were more likely to self-report discontinuing treatment. Some women were struggling to cope with the side effects but did not want to discontinue treatment due to their strong beliefs in the necessity of tamoxifen. In order to cope with this and control the side effects, they skipped or halved doses. Patients in this study fell into one of these three distinct groups, but this may not generalise to all women.

Whilst some women were happy with their decision to discontinue treatment, and felt it was the right choice for them, others were keen to continue treatment but were struggling with side effects, and some did not fully understand how tamoxifen helps them. These latter two groups may benefit from interventions informed by the results of this study, such as detailing how tamoxifen works to reduce recurrence or self-management and support for side effects. Furthermore, if we can intervene early to support women with side effects, we may be able to prevent patients reaching the stage where it is no longer worth it for them to take tamoxifen.

Many patients felt that they were not given enough information about tamoxifen. If women went to their HCPs for help, they were often not given support in managing their side effects. Additionally, some women felt that their HCPs did not validate their experience of side effects. Side effects were consistent with what has been documented in previous

literature (Boehm et al., 2009; Garreau, Delamelena, Walts, Karamlou, & Johnson, 2006). Some side-effects had a significant impact on women's QOL, prohibiting them from working or socialising. The majority of women did not know how to manage these side effects, which exacerbated their impact on social, physical and emotional functioning. In extreme cases, the accumulation of unmanaged side effects led to patients feeling depressed and suicidal.

Whilst the data was analysed using an inductive approach and a reflexive process was used to avoid any pre-conceived knowledge and biases, the themes that were generated fit well within the Self-Regulation Model of Illness Perceptions (Leventhal, Diefenbach, & Leventhal, 1992) and the Necessity Concerns Framework (Horne & Weinman, 1999). Illness perceptions, such as perceptions around the risk of recurrence, do seem to impact on adherence, as do beliefs about the necessity of tamoxifen. The Necessity-Concerns Framework suggests that when deciding whether to take medication, patients weigh up their concerns against their beliefs regarding how necessary the medication is for them (Horne & Weinman, 1999). These beliefs have been shown to relate to HT adherence and persistence (Fink, Gurwitz, Rakowski, Guadagnoli, & Silliman, 2004; Jacob Arriola et al., 2014). This study contributes new understanding by moving beyond the generic model and showing the specific beliefs held by these patients and how they influence behaviour. It highlights the strength of some women's necessity beliefs and shows the variability of the cost-benefit analysis across women; some women's' desire to stay alive were so strong that they reported tolerating any side effects whereas others would rather not live with the side effects despite the risk of recurrence. Women may hold such strong necessity beliefs because the outcome of not taking the medication is so serious.

Women also had concerns about tamoxifen, but these seemed to focus almost exclusively on the experience of side effects, rather than other common concerns such as dependency. The beliefs women held were also consistent with the Self-Regulation Model of Illness Perceptions (Leventhal, Diefenbach, & Leventhal, 1992), which proposes that coping behaviours such as adherence are influenced by patient's beliefs about their illness (Chilcot, Wellsted, & Farrington, 2010). Patients in this study held strong beliefs regarding the extent to which tamoxifen could control their risk of cancer. The results of this study give interesting insight into the specific illness perceptions held by breast cancer survivors taking tamoxifen. These women did not perceive themselves as currently having cancer, but did feel at risk of a recurrence and struggled to cope with the uncertainty surrounding this. This fear of recurrence is what motivated women to continue taking their tamoxifen.

This study suggested that side effects can cause women to discontinue treatment, which has been shown in several quantitative studies (Demissie, et al., 2001; Simon, Latreille, Matte, Desjardins, & Bergeron, 2014; Wouters et al., 2014). However, there is an inconsistent relationship between side effects and adherence, with some studies finding no significant effects (Fink, et al., 2004; Kostev et al., 2013). The results from this study suggest that adherence is not just related to the experience of side effects, but how women weigh these up against their beliefs; that is that just the experience of side effects is not sufficient to cause non-adherence. This may explain the inconsistent effects found previously. Furthermore, adherence rates may be related more to the perceived impact of side effects, than the side effects themselves as evidenced by the fact that nearly all of the women experienced side effects to some extent but most persisted with their tamoxifen treatment. This weighing up process is also supported by trade-off studies showing that women with more severe side effects needed larger gains in survival to make HT worthwhile (Duric et al., 2005; Thewes et al., 2005).

Previous research has suggested that forgetting is a significant driver in HT non-adherence (Atkins & Fallowfield, 2006). However in this study, forgetting did not seem to be a problem for women. Women who felt that the benefits of tamoxifen outweighed the side effects were motivated to keep taking it every day and established routines which helped them to remember. Women who missed doses reported doing so deliberately, such as taking breaks when on holiday or skipping doses to avoid side effects. Although this is based on self-reported responses and should be treated with caution, non-adherence through forgetting is often more commonly self-reported than deliberately skipping or changing doses. This could be due to socially-desirable reporting and the perception that forgetting is more "acceptable" than deliberately not following a prescription (Atkins & Fallowfield, 2006).

Some women did not feel that the benefits of tamoxifen were worth the reduced QOL, which may be related to the fact that the benefits are hidden and there is no reduction in symptoms which can be attributed to medication taking (Meyer, Leventhal & Gutmann, 1985). The information women receive about their treatment and side effects is therefore incredibly important in increasing their necessity beliefs. All women should be given personalised information, so they are able to make decisions about tamoxifen based on the extent to which it will benefit them. Women also wanted to be warned about what side-effects to expect. Previous research has shown that women who experienced side effects they were not told about were significantly more likely to discontinue HT (Kahn, Schneider, Malin, Adams, & Epstein, 2007). Furthermore, women who receive less information about HT are less likely to initiate treatment (Friese et al., 2013) and more likely to take treatment breaks (Cluze et al., 2012).

Patients also need to be informed about the importance of taking tamoxifen as prescribed. Some women deliberately missed or halved doses and still wanted to appreciate the benefits of tamoxifen. These women may not be aware that by reducing the dosage of tamoxifen they are reducing the effectiveness (McCowan, et al., 2008). If they were more educated about the implications of taking less than 80% of the prescribed dose, they may be more motivated to take it as prescribed.

Qualitative research provides a unique opportunity to understand a clinical problem from the patient's perspective. This study had a large diverse sample, recruited through a range of locations and used in-depth interviews which enhance the richness and generalisability of the results. However, there were several limitations. Firstly, women who had chosen not to initiate tamoxifen were not included in the study. Future research should interview these women to understand the reasons behind their decision. Second, the study may have under-represented women who were non-adherent as there may be a selection bias where non-adherent women were less likely to respond to advertisements. However, there is reason to believe that women with negative experiences may also be biased to respond to advertisements. Twenty nine percent of participants were either non-persistent or non-adherent, but research shows this figure could be as high as 50% (Partridge, Wang, Winer, & Avorn, 2003). Including more women who were non-adherent or non-persistent may have given further insights into what drives these behaviours. However, interviewing adherent women gives interesting insight into what motivates women to keep taking treatment, even when they are experiencing severe side effects. Finally, several of the women in the study had discontinued tamoxifen or had been taking it for some time and there may be issues of recall bias.

Clinical implications

Women who are given clear information about tamoxifen and how it might personally benefit them are in a much better position to make a decision on whether it is worth it for them to take it. Whilst for some women it is a logical choice to discontinue tamoxifen, others are keen to continue treatment but cannot cope with the side effects. Supporting these women may stop them from reaching the point where they have to discontinue. For women who are not fully informed, increasing necessity beliefs by providing information may help to improve adherence rates and allows women to make an informed decision about continuing treatment. Patients should also be informed about the importance of taking tamoxifen as prescribed.

Conclusions

This study suggests that the main reason women are non-adherent or non-persistent with tamoxifen is because they are struggling with the side effects and they do not believe that the benefits of the treatment outweigh the side effects. Women expressed a need for more information about tamoxifen. Supporting women with their side effects and providing more information on the benefits of tamoxifen should help to increase adherence and improve clinical outcomes.

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4.3. Summary

The results from this study will help to inform the development of a psycho-educational self-management intervention to improve tamoxifen adherence in BCS. Whilst some women were happy with their decision to stop taking tamoxifen, others were struggling with this decision. They wanted to discontinue treatment to avoid the side effects but they were not prepared to lose the benefits of tamoxifen. This suggests that supporting these women to effectively cope with their side effects may help them to continue with tamoxifen treatment without detriment to their quality of life. Furthermore, helping women to manage their side effects may prevent women from reaching the stage where it is no longer worth it for them to take tamoxifen. The qualitative study also suggested that increasing necessity beliefs may improve adherence rates, supporting the results seen in the systematic review. Several psychoeducation based interventions have shown success at increasing necessity beliefs (Bender et al., 2010; Petrie, Perry, Broadbent & Weinman, 2012). Participants also discussed a lack of support and information from their HCPs. This suggests there is a need for a self-management intervention to provide the support that women may feel is lacking from their HCPs. This is supported by the relationship between patient/physician relationship and adherence shown in the systematic review, and is especially important as the NHS moves away from regular follow up towards Open Access Follow Up, where patients may receive less regular unprompted support from their physicians. The results from the qualitative study also showed that the majority of participants' concerns focussed on side effects. More generic concerns such as dependency or tolerance did not seem relevant in this population. One additional concern which was identified was the risk of endometrial cancer, which will be addressed in the intervention.

The qualitative results show that understanding how women weigh up their beliefs about tamoxifen may be more important than just investigating side effects. Some women will continue to take tamoxifen regardless of their side effects, whereas others may discontinue once they experience any side effects. Their reaction to these side effects depends on how necessary they perceive the tamoxifen to be, and how motivated they are to avoid a recurrence. This may explain the inconsistent relationship found between side effects and adherence in the systematic review. The inconsistency may be due to the fact that side effects will not cause non-adherence if the patient has high enough necessity beliefs. Taking both studies together suggests that whilst side effects are a key driver for non-adherence, the beliefs women hold about tamoxifen or breast cancer may be more important predictors. This provides important information to help with supporting these patients clinically, and will also help with the design and interpretation of future quantitative studies.

The qualitative study also supports the findings of the systematic review by suggesting that medication beliefs are a key determinant of non-adherence. These results support both the Necessity Concerns Framework (NCF) and the Common Sense Model (CSM), by identifying key illness and treatment beliefs which appear to be associated with non-adherence to tamoxifen. Furthermore, the qualitative results suggest that patients may be driven by their fear of a recurrence, a finding which was not seen consistently in the systematic review. The systematic review presented an inconsistent picture of predictors of non-adherence, and whilst the qualitative study has helped to understand some of these factors from the patient's perspective, this was not a generalizable study and it does not allow for examination of effect size or significance of relationships. Therefore, there is a need to test the variables identified in the previous studies in a quantitative analysis. Moving beyond the previous studies to a large longitudinal questionnaire study helps to determine the strength of the relationship between key determinants and non-adherence. Furthermore, the cross-sectional analysis allows us to test key elements from the CSM and Theory of Planned Behaviour (TPB) to determine which model provides more explanation of non-adherence and which factors remain significant over and above clinical or demographic variables. The majority of studies in the systematic review have failed to use theoretical models when investigating non-adherence. These models provide a structured framework for investigating key determinants of non-adherence and help with development of interventions (Holmes et al., 2014). Using a theoretical framework may increase the effectiveness of interventions to improve adherence (Horne et al., 2005). As discussed in Chapter 2, studies have shown that both the CSM and the TPB have been useful in predicting medication non-adherence, yet no published studies have applied these theories to tamoxifen non-adherence. As well as this evidence, the qualitative results supported the use of the CSM and the NCF, by showing that womens' beliefs about their medication and their cancer are related to non-adherence. Therefore, there was a need to investigate the utility of key aspects of these models to explain tamoxifen non-adherence. This analysis is presented in Chapter 6. The next chapter, Chapter 5, presents the modification of the Revised Illness Perceptions Questionnaire (IPQ-R) for use in BCS.

5. Modification of the illness perceptions questionnaire for use in breast cancer survivors

5.1. Chapter Overview

Illness perceptions are a key component of the Common Sense Model of Illness Representations (CSM) and have been reliably associated with medication adherence in a range of conditions (Brewer et al., 2002; Chen et al., 2011; Daleboudt et al., 2011; Horne & Weinman et al., 2002; Van der Have et al., 2016). These illness perceptions are usually measured using the Illness Perceptions Questionnaire (IPQ; Weinman et al., 1996), the Brief IPQ (Broadbent et al., 2006) or the Revised Illness Perceptions Questionnaire (IPQ-R; Moss-Morris et al., 2002). These questionnaires were developed and validated in a range of different long term conditions, and the authors recommend that they are modified for use in different illnesses due to the unique characteristics and aetiology of each illness (Moss-Morris et al., 2002). However, despite these recommendations, any modifications made are usually very minor, such as adding relevant symptoms or causes or making small changes to the language. These minor modifications will most likely fail to pick up the unique characteristics of different illnesses. Therefore there is a need for the questionnaire to be tailored to the specific patient population. This need is particularly strong in a sample such as Breast Cancer Survivors (BCS), where patients may not feel that they currently have an illness, due to the fact that they have been treated for their breast cancer and are now controlling the risk of a recurrence. Several studies have suggested that breast cancer survivors are in a conflicting state where they may feel neither sick nor healthy (McKenzie & Crouch, 2004; Powers et al., 2016). Whilst many women see themselves as survivors, and do experience a range of psychosocial and medical implications following treatment (Bowman et al., 2003; Fallowfield & Jenkins, 2015), many also feel that they have put the active illness behind them. The IPQ-R was developed for patients with an active illness and with relevant symptoms to control. It was therefore expected that BCS would have difficulty answering some of the questions on the IPQ-R relating to active illness and symptom control. For example, the IPQ-R asks participants the extent to which they agree or disagree with the statement "*my breast cancer will last a long time*". It was anticipated that women may have difficulty interpreting and answering items like this, as they may not feel that they currently have breast cancer. Similarly, items around symptom control such as "*there is a lot I can do to control my symptoms"* or "*my symptoms come and go in cycles"* may need to be modified, as women may confuse these symptoms with the side effects of their medication. This chapter presents the modification of the IPQ-R for use in BCS taking tamoxifen.

5.2. Published paper

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Article title: Measuring illness representations in breast cancer survivors (BCS) prescribed tamoxifen: Modification and validation of the Revised Illness Perceptions Questionnaire (IPQ-BCS)

Authors: Zoe Moon, Rona Moss-Morris, Myra S Hunter, Sophie Carlisle, Lyndsay D Hughes

Health Psychology Section, Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

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Keywords: illness perceptions; scale validation; confirmatory factor analysis; IPQ-R; breast cancer; tamoxifen

Corresponding author:
Lyndsay D Hughes
Health Psychology Section,
Institute of Psychiatry, Psychology & Neuroscience,
5th Floor Bermondsey Wing, Guy's Hospital,
London SE1 9RT, UK
Email lyndsay.hughes@kcl.ac.uk

Measuring illness representations in breast cancer survivors (BCS) prescribed tamoxifen: Modification and validation of the Revised Illness Perceptions Questionnaire (IPQ-BCS)

Objective: The Revised Illness Perceptions Questionnaire (IPQ-R), widely used to assess illness perceptions, may fail to measure unique characteristics of different illnesses. This study modified and validated the IPQ-R for breast cancer survivors to provide detailed understanding of the specific illness perceptions held by these patients.
Design: Initial modifications were made following qualitative interviews and were revised in a think-aloud study. The modified scale was tested in 753 breast cancer survivors prescribed tamoxifen. Modifications included adding a tamoxifen consequences scale and adapting the timeline scales to measure beliefs around risk of recurrence and cure. A confirmatory factor analysis was conducted on the modified questionnaire and an exploratory factor analysis on the causal beliefs scale. Test–retest reliability, internal consistency and construct validity were also examined.
Results: The proposed eight-factor structure showed acceptable model fit, with high loadings and good reliability for all subscales. Correlations between subscales were consistent with theory and previous research.
Conclusions: The IPQ-BCS is valid and reliable, and provides unique understanding of specific perceptions held by this population, including beliefs surrounding risk of recurrence and consequences of ongoing hormonal treatment. Identifying these perceptions will aid development of interventions targeting depression, fear of recurrence and medication non-adherence.
Keywords: illness perceptions; scale validation; confirmatory factor analysis; IPQ-R; breast cancer; tamoxifen

Introduction

Illness representations or perceptions, which form part of the Common Sense Model of Self-Regulation (CSM; Leventhal, Diefenbach, & Leventhal, 1992), predict a range of outcomes, including quality of life (QOL) (Petrie, Jago, & Devcich, 2007), fatigue (Jopson & Moss-Morris, 2003) and poor physical and mental health (Frostholm et al., 2007; Whittaker, Kemp, & House, 2007). The CSM proposes that patients' coping behaviours, such as adherence, are guided by their cognitive and emotional representations of their illness. Cognitive representations include common sense beliefs about the illness identity (the symptoms/label associated with the illness), the cause(s), consequences, timeline and controllability of the illness. Patients also have emotional representations, such as fear, which guide how they respond to the illness. Finally, patients have a metacognitive

perception of the coherence of their illness representations (Moss-Morris et al., 2002). The development of the Illness Perceptions Questionnaire (IPQ; Weinman, Petrie, Moss-Morris, & Horne, 1996), the Brief Illness Perceptions Questionnaire (Brief IPQ; Broadbent, Petrie, Main, & Weinman, 2006) and the Revised Illness Perceptions Questionnaire (IPQ-R; Moss-Morris et al., 2002) allowed researchers to quantify illness representations and increased empirical research on the role of illness perceptions in areas such as coping, medication adherence and health outcomes.

The IPQ-R has shown good internal reliability and test–retest reliability, as well as sound discriminant, known group and predictive validity (Moss-Morris et al., 2002). However, it was developed as a generic scale for use across different illness groups and therefore may not provide insight into the unique beliefs of different patient groups (French &Weinman, 2008). Whilst the authors of the IPQ-R recommend that the scale is modified for use in different contexts (Moss-Morris et al., 2002), validated modified versions are currently lacking. Researchers often rely on very minor modifications such as adding symptoms or causes which may not tap into illness-specific beliefs. Thinkaloud studies have shown that patients can struggle to answer questions on the IPQ. Patients enrolled in physiotherapy or a preoperative exercise programme had some difficulty completing the Brief IPQ and occasionally misinterpreted questions (van Oort, Schroder, & French, 2011). Another study showed that patients with type 2 diabetes had difficulties with the concepts of cure and symptoms and misunderstood the negative wording on some questions on the IPQ-R (McCorry, Scullion, McMurray, Houghton, & Dempster, 2013b).This highlights the need to explore the face validity of IPQ-R items in different groups of patients and to test the face validity of modifications using thinkaloud methods.

One patient group for whom modifications may be particularly pertinent are breast cancer survivors (BCS). There are around three million BCS living in the US and another 200,000 women are diagnosed with breast cancer every year (American Cancer Society, 2014). These patients have completed their active treatment and may no longer consider themselves to be ill, although continued therapy and monitoring are required. They may therefore struggle to answer questions on the IPQ-R about current illness or current symptom control. However, BCS experience a myriad of psychosocial issues and measuring illness perceptions is relevant to understanding these ongoing reactions to their previous cancer. For example, around a quarter of BCS experience depression or fatigue, and up to 70% show clinical levels of fear of cancer recurrence (FCR) (Cvetković & Nenadović, 2016; Servaes, Gielissen, Verhagen, & Bleijenberg, 2007; Thewes et al., 2012). Others also struggle to cope with long-term hormonal therapy such as tamoxifen, which is prescribed for up to 10 years as adjuvant treatment for women with oestrogen receptive positive breast cancer (about 75%

of all breast cancers; Harrell et al., 2007). Whilst tamoxifen is one of the most effective systemic treatments available for breast cancer, it can cause unpleasant side effects (Garreau, Delamelena, Walts, Karamlou, & Johnson, 2006) and both non-adherence and non-persistence rates are often as high as 50% within five years of treatment (Hershman et al., 2010; Kostev, Haas, & Hadji, 2012; Owusu et al., 2008). Non-adherence to tamoxifen is associated with significantly increased risk of recurrence and mortality (Barron, Cahir, Sharp, & Bennett, 2013; Hershman et al., 2011; Makubate, Donnan, Dewar, Thompson, & McCowan, 2013). However, little is known about how illness perceptions and beliefs may affect adherence in this population.

An IPQ modified to address beliefs about a past illness, possibility of recurrence and ongoing adjuvant treatment will allow researchers to investigate illness representations alongside BCS-specific coping (including adherence) and psychological outcomes. The CSM has been suggested as a useful framework for understanding FCR (Fardell et al., 2016) and other breast cancer survivorship issues (Kaptein et al., 2015). Further, identifying illness perceptions idiosyncratic to BCS could aid development of interventions, which have the potential to improve psychological well-being and QOL (Simard et al., 2013).

This study aimed to modify the IPQ-R for use with BCS. We focused specifically on women taking tamoxifen in order to get a more homogenous sample and to tap into illness beliefs specific to adjuvant therapy. Following advice from French and Weinman (2008), we used a mixed methods approach to modify and validate the questionnaire. The specific objectives were:

(1) To conduct qualitative interviews based on the CSM to elicit key beliefs held by BCS taking tamoxifen;

(2) To use these interviews to develop a modified version of the IPQ-R (the IPQ-BCS);

(3) To test the face validity of this modified questionnaire using think-aloud interviews and modify further if indicated;

(4) To assess the factor structure, internal consistency and test–retest reliability of the modified IPQ-BCS in a large cross-sectional study of BCS;

(5) To assess construct validity of the new subscales using inter-correlations between subscales and relationships between subscales and psychological variables (beliefs about medications and distress). It was hypothesised that IPQ-R subscales would show correlations similar to that found in previous research (Hagger & Orbell, 2005; Moss-Morris et al., 2002). We hypothesised that distress would be associated with higher consequences, identity, emotional representations and risk of recurrence beliefs; that tamoxifen necessity beliefs would correlate with treatment

control; and that tamoxifen concerns would correlate consequences and identity beliefs.

Method

The study was approved by the Northampton National Research Ethics Committee (REF 14/EM/1207).

Qualitative study

Participants and procedure

Participants were recruited through an oncology clinic in a London hospital and through online advertisements, as part of a larger study investigating women's experiences of taking tamoxifen. Patients were eligible if they were female, over the age of 18 and had been prescribed tamoxifen post primary breast cancer. Patients were told about the research by their clinician, and if interested, they were introduced to a researcher and given an information sheet. Women who responded to online advertisements were screened for eligibility and given information about the study.

A follow-up call was made two days later to arrange an interview. This was part of a larger qualitative study to explore women's experiences of taking tamoxifen. Patients were interviewed face to face or over the telephone. Informed consent was taken prior to each interview. Interviews were recorded and transcribed verbatim. Participants were first asked a series of general questions about their experience of tamoxifen, before being asked specific questions regarding their illness perceptions for modification of the IPQ-R (See Table 1 for interview schedule). Thirty-two women took part in the larger qualitative study, of whom 18 were asked the additional questions specifically relating to the modification of the questionnaire. Data collection for these additional questions ceased once data saturation was reached and only these questions were analysed in this study. Thus, data from 18 women were analysed. Participant demographics are shown in Table 2.

Item development

Interviews were analysed using deductive analysis. Using the CSM as a framework, themes were generated around prevalent beliefs and perceptions. Changes to the questionnaire were made to reflect the language used by participants. A key theme was that women did not identify as currently having breast cancer. All questions were amended to avoid asking women about their breast cancer in the present tense. Original and amended items are shown in Supplementary Material (Appendix D).

A second theme suggested women attributed few symptoms to breast cancer. Therefore, the identity scale was amended to assess symptoms which were (a) attributed to breast cancer, (b) to tamoxifen treatment and (c) to their previous/other treatment.

Table 1. Interview schedule for qualitative interviews

(1) Are there any specific side effects that you have experienced? ▪ *Ones that your doctor did not tell you about?*
(2) Do you believe that your previous treatment has cured your breast cancer?
(3) Do you still experience ongoing effects from your previous treatment (chemo, surgery, radio)?
(4) Do you still see yourself as having breast cancer? ▪ *What is your relationship with breast cancer?*
(5) What do you see as the main consequences of Tamoxifen?
(6) What do you see as the main consequences of breast cancer?
(7) Do you think that tamoxifen is preventing a risk of recurrence?
(8) What else might be impacting a risk of recurrence?
(9) Is there anything else you can do to control this (prevent risk of recurrence)?

Analysis of the interviews elicited specific tamoxifen-related symptoms. Ten new symptoms, such as hot flushes and change in sex drive, were added to the original list of 14 symptoms in the core version of the IPQ-R (See Table 3 for list of additional symptoms). When asked about control, consequences and causes, women tended to discuss their risk of recurrence instead of their breast cancer. Therefore, to effectively assess control beliefs, the personal and treatment control subscales were amended so that the word 'illness' was replaced with 'risk of recurrence'. The treatment control items were asked specifically in relation to tamoxifen. In addition to the existing illness consequences scale, a new scale was added to assess the consequences of taking tamoxifen, as this was a dominant theme identified in the interviews.

With regard to timeline beliefs, the interviews showed that women did not have symptoms which come and go. The cyclic timeline scale was removed and a new scale was added to assess risk of recurrence. Likewise, the timeline acute/chronic scale was amended to assess the extent to which women believe that their breast cancer is cured, as the interviews showed that these beliefs were much more pertinent than beliefs around the chronic nature of breast cancer itself. The coherence scale was modified to measure understanding of tamoxifen treatment rather than breast cancer. Finally, as women discussed fear around risk of recurrence rather than fear around breast cancer, the emotional representations scale was amended to reflect this. The cause scale was modified by adding breast cancer-specific causes such as hormonal influence and removing causes which were not applicable. Examples of changes to specific items are shown in Table 3.

Table 2. Demographics characteristics of participants.

	Interview study n=18	*Think aloud study n=8*	*Factor analysis n=753*	*Test-retest reliability n=48*
Age *mean (SD)*	53 (10.2) Range 36 – 63	53 (9.2) Range 37 – 63	53 (10.5) Range 30 – 91	56 (10.3) Range 38 - 82
Race *n (%)*				
White British	13 (72%)	8 (100%)	654 (87%)	44 (94%)
Other	5 (28%)	0 (0%)	99 (13%)	3 (6%)
Age left full time education *n (%)*				
16 or under			304 (40%)	25 (52%)
Over 16			449 (60%)	23 (48%)
Menopausal status at diagnosis *n (%)*				
Pre-menopausal	4 (22%)	2 (25%)	414 (55%)	
Menopausal	2 (11%)	1 (12.5%)	86 (11%)	
Post-menopausal	9 (50%)	4 (50%)	202 (27%)	
Unsure	3 (17%)	1 (12.5%)	33 (4%)	
Months since breast cancer diagnosis *Mean (SD)*	36 (25) Range 1 year – 5.5 years	25 (19) Range 1 year – 6 years	33 (24) Range 2 months – 16 years	45 (25) Range 1 month – 9 years
Stage at diagnosis *n (%)*				
Stage I			321 (43%)	
Stage II			339 (45%)	
Stage III			93 (12%)	
Previous treatment *n (%)*	12 (67%)	5 (63%)	483 (64%)	
Lumpectomy	2 (11%)	1 (13%)	249 (33%)	
Single mastectomy	1 (5%)	2 (25%)	44 (6%)	
Double mastectomy	7 (44%)	3 (38%)	384 (51%)	
Chemotherapy	15 (83%)	6 (75%)	557 (74%)	
Radiotherapy				

Note. SD, Standard deviation. Blank spaces indicate incidences where data was not collected.

Think-aloud study

After item modification, a think-aloud study was conducted to examine if items on the new IPQ-R were being understood and interpreted in the expected way. Eleven women from the interview study were invited to take part in the think-aloud study and eight agreed. Think-aloud studies involve patients verbalising their thought process as they answer the questionnaire (Ericsson & Simon, 1998). These methods have been used previously to examine questionnaires assessing illness perceptions (van Oort et al., 2011), theory of planned behaviour (French, Cooke, McLean, Williams, & Sutton, 2007) and QOL (Westerman et al., 2008).

Table 3. Examples of changes made to the original IPQ-R.

	Previous item	New item
Identity scale		Change in libido, hot flushes, leg cramps, loss of concentration, night sweats, joint pain, vaginal dryness/itchiness/discomfort, feeling down, changes to periods, feeling lightheaded
Timeline acute / chronic (cure)	My illness will last for a long time	My breast cancer is cured
Breast cancer consequences	My illness has major consequences on my life	My breast cancer still has major consequences on my life
Tamoxifen consequences	-	I can't function normally whilst taking tamoxifen
Personal control	My actions will have no effect on the outcome of my illness	My actions will have no effect on the risk of cancer coming back
Treatment control	Tamoxifen treatment can control my illness	Tamoxifen treatment can control my risk of recurrence
Coherence	My breast cancer is a mystery to me	Tamoxifen is a mystery to me
Timeline cyclical (risk of recurrence)	I go through cycles in which my breast cancer gets better and worse	There is a good chance my cancer will come back
Emotional representations	I get depressed when I think about my breast cancer	I get depressed when I think about my risk of recurrence
Causes		Hormonal influence, exercise

Participants were asked to complete the modified IPQ-BCS and to verbalise everything they were thinking as they were completing the questionnaire. If they were quiet for a long period of time, they were prompted to think aloud as they were considering the question. The think-aloud sessions were conducted over the telephone and participants consented to be audio recorded.

The think-aloud interviews showed that women could understand the questionnaire and that they found it relevant and applicable. However, several issues were identified which led to further modifications. The instructions to both the identity and cause scales were modified to improve their clarity. A few participants remarked that some items in the personal and treatment control scales were worded too severely and that they were unsure how to answer them. Therefore, the items were amended to reflect this. Several other items were revised slightly to enhance the chance they would be applicable for all participants or to ensure they were being correctly interpreted. Some women remarked on the repetitiveness of questions, so where possible items were deleted (See Supplementary Material).

Quantitative study

Participants and procedure

Participants were recruited through oncology clinics at 25 NHS Trusts throughout England and through online advertisements. Patients were eligible if they had a diagnosis of primary breast cancer and if they had been prescribed tamoxifen. Participants had to be female and over the age of 18. Patients were approached by a member of their clinical team during a routine clinic appointment or received an invitation in the post from their clinical team. They were given information about the study along with the questionnaire and a return envelope. After providing informed consent, participants either completed the questionnaire in the clinic or took it home to return to the researcher. Participants who were recruited online responded to an advert and after being screened for eligibility, were sent information about the study along with a link to an online questionnaire. Participants gave informed consent whilst completing the online questionnaire. A separate sample was recruited to assess the test–retest reliability of the IPQ-R. This sample was recruited from four NHS Trusts. Participants were given information about the study from the clinical team and once consented, they completed the first questionnaire in clinic. Participants were either posted the second questionnaire or given a link to complete it online two weeks later, whichever was their preference. Telephone reminders were made if the second questionnaire had not been returned within one week.

Measures

Modified IPQ-R (IPQ-BCS). Participants completed the modified version of the IPQ-R (IPQ-BCS), which included subscales measuring identity, cure beliefs, risk of recurrence, tamoxifen consequences, breast cancer consequences, personal control over recurrence, tamoxifen control, coherence, emotional representations and causes. All questions were scored on a five-point Likert-type scale ranging from Strongly Agree to Strongly Disagree with the exception of the identity scale where participants ticked each column to indicate if they experienced that symptom. Each subscale included four items, with the exception of cure beliefs, tamoxifen consequences and emotional representations, which included five items. The identity subscale was calculated by totalling the number of symptoms which were attributed to tamoxifen. Symptoms which were added to the original list of symptoms are shown in Table 3.

Hospital Anxiety and Depression Scale. The Hospital Anxiety and Depression Scale (HADS) is a 14-item scale measuring depression and anxiety (Zigmond & Snaith, 1983). The total distress scale was used in this study, as a large meta confirmatory factor analysis (CFA) has shown evidence of a strong general HADS factor rather than two distinct

subscales (Norton, Cosco, Doyle, Done, & Sacker, 2013). Each item is scored on a scale of 0–3, with higher scores reflecting higher levels of distress. The HADS has shown good reliability in patients with breast cancer (Matthews et al., 2014; Stanton, Petrie, & Partridge, 2014).

Beliefs about Medicines Questionnaire. The Beliefs about Medicines Questionnaire (BMQ)-Specific measures beliefs surrounding the necessity of taking medications and concerns about adverse effects (Horne, Weinman, & Hankins, 1999). The word medication was replaced with the word tamoxifen for all items. Each item is rated on a five-point Likert-type scale. A higher score on each subscale indicates stronger necessity or concern beliefs. The scale has been used many times in BCS with Cronbach's alpha values of .79–.86 and .72–.84 for the necessity and concerns scale, respectively (Bender et al., 2014; Corter, Findlay, Broom, Porter, & Petrie, 2013; Jacob Arriola et al., 2014).

Statistical analysis

Missing data were less than 5% and were replaced using mean substitution. A CFA was conducted on the modified IPQ-BCS using Mplus version 7 to test the hypothesised model of eight subscales (cure beliefs, tamoxifen consequences, risk of recurrence, breast cancer consequences, personal control, treatment control, coherence and emotional representations). CFA is the gold standard method for evaluation of construct validity in psychometric tests (Hu & Bentler, 1999). The CFA was conducted using weighted least squares with means and variances corrected, as the data were measured on an ordinal categorical scale. Multiple indices were used to assess model fit. Chi-squared was not used as it is sensitive to sample size (Byrne, 2001). The comparative fit index (CFI), root mean square error of approximation (RMSEA) and Tucker– Lewis index (TLI) were used. CFI or TLI values of greater than .95 suggest acceptable model fit (Hu & Bentler, 1999). RMSEA values of .08 indicate reasonable fit and values of under .06 indicate good fit (Hu & Bentler, 1999). The reliability of each subscale was tested using Cronbach's alpha. Test–retest reliability was assessed using intraclass correlation of each subscale at baseline and two-week follow-up. Discriminant validity was assessed using inter-correlations between IPQ-R dimensions. Construct validity was assessed by examining the correlations between IPQ-R dimensions and additional variables (beliefs about medications and distress). It is recommended that the causal attribution scale be examined in an exploratory fashion (Dempster & McCorry, 2012); therefore, exploratory factor analysis (EFA) was used as it does not specify an underlying factor structure. Item frequencies were visually inspected and items were removed if the majority of participants did not see them as a cause. An EFA was then conducted using the SPSS R-menu for ordinal factor analysis based on polychoric correlations (Basto & Pereira, 2012). The number of factors to retain was assessed using

parallel analysis (Horn, 1965). The factor analysis was conducted using Maximum Likelihood extraction and Geomin Q-Q rotation.

Results

Data were collected from 753 participants. Participants were all female and had been diagnosed with Stage I–III breast cancer (Table 2). Mean age was 53 (SD = 10.5) and participants were on average 33 months post breast cancer diagnosis (SD = 24, range 2 months–16 years).

Confirmatory factor analysis

The sample size exceeded the requirements of at least three cases per item (Tabachnick & Fidell, 2007). Visual inspection of the data showed the items generally correlated as expected within the eight subscales, indicating that a CFA was appropriate. The 35-item IPQ-BCS showed acceptable model fit (RMSEA = .08, 95% CI = .08–.09, CFI = .95, TLI = .94). In order to reduce the length of the scale, one item (with the lowest factor loading) was removed from each of the three subscales with five items (tamoxifen consequences, cure beliefs and emotional representations). Removing these items did not change the overall model fit, and therefore this briefer questionnaire is preferred where all subscales have four items. Table 4 shows the factor loadings for each of the items under each of the subscales. Factor loadings were all well above the required threshold of .40 (Ford, MacCallum, & Tait, 1986), ranging from .63 to .95.

Internal and test–retest reliability

All scales showed excellent reliability, with Cronbach's alpha values ranging from .76 to .92 (Table 4). Test–retest reliability was tested in a separate sample of 48 women. Participants completed the questionnaire twice; on average, 18 days apart (range 11–31). The intra-class correlation coefficients for each scale ranged from .77 to .94, indicating excellent test–retest reliability (Table 4).

EFA on cause items

Item frequencies and correlations were explored visually and two items were removed from the EFA. Item 3 (A germ or virus) was removed as it did not correlate with other items and only 5% of participants agreed that it might be a risk factor for recurrence. Item 12 (smoking) was also removed, as only 24% of participants provided data for this question. Hormonal influence was the strongest item, with 81% of participants agreeing that it was a risk factor.

Parallel analysis was used on 11 causal items to assess the number of factors to retain, and indicated a three-factor solution, explaining 46% of the total variance. Factor loadings are shown in Table 5. The first factor, labelled psychological attributions, included items relating to stress, worries and emotional state. The second factor, labelled health behaviours, included items such as diet and eating habits and exercise. These two factors showed good reliability (.85 and .72, respectively). The final factor included item 11 (ageing) and item 13 (hormonal influence). However, hormonal influence had a factor loading of below .4 and the reliability of the factor was very low (.44). Therefore, these items might be best considered individually and not as part of a subscale. Item 2 (runs in the family) and item 5 (chance or bad luck) did not load onto any factors.

Examination of the identity scale

Each symptom was experienced by at least 13% of participants. Over 40% of participants had experienced pain, weight loss/gain, hot flushes, night sweats, fatigue, sleep difficulties, joint pain and loss of sex drive. Patients experienced on average 7.8 symptoms (SD = 5.9). Symptoms were more commonly attributed to tamoxifen (mean = 5.8, SD = 4.9) than to breast cancer (mean = 2.1, SD = 3.2) or previous/other treatment (mean = 2.0, SD = 3.6). As symptoms were rarely attributed to breast cancer, identity was represented by the total number of symptoms attributed to tamoxifen. All symptoms were most commonly attributed to tamoxifen, with the exception of pain which was attributed to breast cancer by 29% of participants and to tamoxifen by 14% of participants. Hot flushes were the most common symptom attributed to tamoxifen (65%), followed by night sweats (55%), weight loss/gain (41%), joint pain (37%), fatigue (35%), leg cramps (35%) and vaginal dryness, itchiness or discomfort (35%). These results provide support for the validity of the symptoms included in the scale as well as the different sources of attribution.

Table 4. Confirmatory Factor Analysis of the eight-factor IPQ-R.

	1	2	3	4	5	6	7	8	Symptoms attributed to tamoxifen	Causes
Cure										
My treatment has been effective in curing my breast cancer	**0.74**									
I no longer have breast cancer	**0.89**									
My breast cancer is cured	**0.85**									
I still see myself as having cancer	**0.81**									
Breast cancer consequences										
My breast cancer still has major consequences on my life		**0.87**								
My breast cancer currently does not have much effect on my life		**0.66**								
I still experience long lasting effects from my original treatment for breast cancer		**0.69**								
My breast cancer currently causes difficulties for those who are close to me (e.g. emotional difficulties)		**0.75**								
Tamoxifen consequences										
Tamoxifen has major consequences on my life			**0.63**							
I can't function normally whilst taking tamoxifen			**0.89**							
Taking tamoxifen has had an impact on those around me			**0.88**							
My work / social life has been affected by taking tamoxifen			**0.95**							
Risk of recurrence										
There's a good chance my cancer will come back				**0.91**						
I expect to have a recurrence of cancer in the future				**0.95**						
I am extremely likely to have a recurrence				**0.92**						
The chance of my cancer coming back is low				**0.72**						

	1	2	3	4	5	6	7	8	Symptoms attributed to tamoxifen	Causes
Personal control										
There are things I can do to stop the cancer coming back					**0.79**					
What I do has an influence on whether my cancer comes back					**0.77**					
There is nothing I can do to help my risk of recurrence					**0.87**					
My actions will have no effect on the risk of cancer coming back					**0.81**					
Tamoxifen treatment can reduce my risk of recurrence						**0.82**				
There is very little that can be done to stop the cancer coming back						**0.84**				
Taking tamoxifen will help stop the cancer coming back						**0.78**				
There is nothing that can help my risk of recurrence						**0.82**				
Coherence										
Tamoxifen is a mystery to me							**0.76**			
I understand how tamoxifen helps prevent cancer recurrence							**0.80**			
I don't understand how much tamoxifen can help me							**0.83**			
I have a good understanding of why I am taking tamoxifen							**0.82**			
Emotional representations										
I get depressed when I think about my risk of recurrence								**0.91**		
I worry about my risk of recurrence								**0.90**		
When I think about the cancer coming back I get upset								**0.90**		
My risk of recurrence makes me feel afraid								**0.94**		
Cronbach's alpha	*0.81*	*0.79*	*0.87*	*0.90*	*0.81*	*0.76*	*0.81*	*0.92*		
Test retest reliability (intraclass correlation coefficient)	*0.92*	*0.92*	*0.92*	*0.87*	*0.77*	*0.91*	*0.91*	*0.94*	*0.86*	*0.87*

Construct validity

Inter-correlations between the IPQ-BCS subscales are shown in Table 6. The direction and size of the correlations are consistent with previous research (Hagger & Orbell, 2005; Moss-Morris et al., 2002), and with what would be expected due to the underlying theory. Tamoxifen consequences and breast cancer consequences were positively correlated. Both consequences scales correlated positively with emotional representations and risk of recurrence and negatively with cure beliefs and treatment control. Cure beliefs had a moderate negative correlation with risk of recurrence. Personal control and treatment control were strongly correlated. Both control scales correlated positively with coherence and cure beliefs and negatively with risk of recurrence. Emotional representations was negatively correlated with cure beliefs and treatment control and positively correlated with risk of recurrence. Identity beliefs correlated positively with tamoxifen consequences, risk of recurrence, breast cancer consequences and emotional representations

Table 5. Exploratory factor analysis on the causal items.

	Factor 1: Psychological attributions	Factor 2: Health behaviours	Factor 3: External causes
Stress or worry	**.771**	.066	-.040
Family problems	**.907**	-.004	-.014
My own emotional state	**.818**	-.009	.096
Diet or eating habits	-.004	**.840**	-.146
My own behaviour	.097	**.622**	.064
Exercise	-.008	**.686**	.059
Pollution in the environment	.212	**.400**	.044
Ageing	.043	.004	**.788**
Hormonal influence	-.097	.209	**.330**
Runs in the family	.076	.076	.112
Chance or bad luck	.002	.067	.239
Cronbach alpha	*0.85*	*0.71*	*0.44*

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Table 6. Correlations between IPQ-R subscales.

		1	2	3	4	5	6	7	8	9
1.	Cure	1								
2.	Tamoxifen consequences	-.14**	1							
3.	Risk of recurrence	-.45**	.23**	1						
4.	Breast cancer consequences	-.31**	.49**	.42**	1					
5.	Personal control	.15**	-.08*	-.24**	-.13**	1				
6.	Treatment control	.23**	-.17**	-.35**	-.22**	.58**	1			
7.	Coherence	.10**	-.10**	-.15**	-.16**	.26**	.44**	1		
8.	Emotional representations	-.24**	.30**	.41**	.54**	-.15**	-.20**	-.16**	1	
9.	Symptoms attributed to tamoxifen	-.12**	.56**	.19**	.36**	.04	.00	.05	.25**	1

**p <0.01, *p<0.05

Table 7. Correlations between IPQ-R subscales, HADS distress and BMQ necessity and concerns.

	Distress	Concerns	Necessity beliefs
Cure	-.20**	-.18**	-.04
Tamoxifen consequences	.53**	.56**	.10*
Risk of recurrence	.31**	.19**	.12**
Breast cancer consequences	.55**	.40**	.15**
Personal control	-.15**	-.08*	.02
Treatment control	-.21**	-.23**	.15**
Coherence	-.15**	-.28**	.07
Emotional representations	.45**	.36**	.23**
Symptoms attributed to tamoxifen	.35**	.43**	.09*

**p <0.001

To further explore the validity of the constructs of the IPQ-BCS subscales, correlations were examined with distress using the HADS and treatment beliefs using the BMQ. These correlations were consistent with hypothesised relationships and supported the construct validity of the IPQ-R dimensions (Table 7). HADS distress correlated positively with identity, consequences, risk of recurrence and emotional representations, and negatively with

cure beliefs and treatment control. BMQ tamoxifen concerns correlated positively with IPQ-BCS tamoxifen consequences, breast cancer consequences, identity and emotional representations, and negatively with treatment control and coherence. BMQ tamoxifen necessity beliefs correlated positively with IPQ-BCS emotional representations and treatment control.

Discussion

This paper developed and validated a modified version of the IPQ-R for use with BCS prescribed tamoxifen. The modified version includes an identity scale which has been modified to assess symptoms attributed to tamoxifen, the original illness consequences scale and a new tamoxifen consequences scale. The timeline acute scale was amended to measure cure beliefs and the timeline cyclical was replaced with a risk of recurrence scale. The personal control, treatment control and emotional representations scales were amended to assess risk of recurrence rather than current cancer. The coherence scale was amended to measure coherence around tamoxifen rather than breast cancer. The 35-item IPQ-BCS showed acceptable model fit, with high factor loadings on the conceptual subscales, and high reliability for all subscales. To decrease participant burden, this was reduced down to a 32-item questionnaire where each subscale has four items. This modification did not affect model fit and the reliability for each scale remained high, demonstrating that the removed items were redundant and that the shortened questionnaire is sufficient to understand these constructs. This modification and validation of the IPQ-R for use in BCS was a vital step in furthering understanding of illness perceptions held by BCS. The qualitative interviews we conducted showed that women would have had difficulty answering questions on the original IPQ-R regarding their current illness and breast cancer symptoms. The think-aloud study showed that items on the modified IPQ-BCS were easy to interpret and to answer.

These results provide support for the CSM and the idea that BCS hold perceptions about their previous breast cancer and ongoing treatment and survivorship. Investigating these illness perceptions will enhance understanding of the psychosocial issues associated with breast cancer survivorship and will help with developing interventions to reduce distress or improve QOL in this population. The modified IPQ-BCS assesses beliefs which would not have been assessed with the original IPQ-R, such as beliefs around risk of recurrence and cure. These beliefs are likely to be relevant to understanding FCR and depression in BCS. The benefit of using the IPQ-BCS to assess FCR is that it allows examination of both perceptions of risk (risk of recurrence scale) and emotional responses to this risk perception (emotional representations scale). Whilst they are correlated, perceptions of the likelihood of a recurrence differ from the emotions (e.g. fear; distress) that women feel in response to this risk perception. Understanding these separate constructs and how they relate to distress or

QOL will aid development of interventions to reduce FCR. Furthermore, the IPQ-BCS allows these risk of recurrence beliefs to be measured alongside other illness perceptions, such as control and consequences, which feed into beliefs around risk of recurrence (Fardell et al., 2016). The IPQ-BCS could be supplemented with a more complex FCR scale which also assesses hypervigilant checking behaviours, functional impairment of FCR or FCR in relation to actual risk.

The IPQ-BCS also measures beliefs regarding tamoxifen treatment specifically, rather than the more generalised treatment control scale included in the IPQ-R. The IPQ-BCS assesses consequences of ongoing tamoxifen treatment as well as breast cancer consequences, and measures treatment control specifically with regard to tamoxifen treatment. This scale could therefore be used to identify illness and treatment beliefs related to non-adherence in this population. Previous studies have found problems with the treatment control subscale of the IPQ-R, such as low reliability and cross-loading of items (Brzoska, Yilmaz-Aslan, Sultanoglu, Sultanoglu, & Razum, 2012; Ibrahim, Desa, & Chiew-Tong, 2011; Moss-Morris et al., 2002). This is likely due to participants being unsure as to which treatment the questions are referring to. Amending this subscale to specifically assess tamoxifen treatment may have overcome these issues, as the IPQ-BCS treatment control subscale showed good reliability and was free from cross-loading. This scale could also be amended to assess treatment control specific to aromatase inhibitors or hormone therapy in general.

The EFA on the cause scale produced three factors. Factor one (psychological attributions) and factor two (health behaviours) showed good reliability. However, some items did not load onto any factors or had low factor loadings. These results are not consistent with the original IPQ-R factor structure (Moss-Morris et al., 2002). However, several papers have found a factor structure which is hard to interpret (Nicholls, Hill, &Foster, 2013; Wittkowski, Richards, Williams, & Main, 2008). In a sample of Greek cancer patients, Giannousi, Manaras, Georgoulias, and Samonis (2010) also found that items 2 (hereditary), 5 (chance or bad luck) and 11 (ageing) did not load onto any factors. Whilst hormonal influence and chance or bad luck did not load onto any factors in this analysis, they were the most consistently endorsed causes and therefore, they should be considered as individual items in future analysis or larger subscales related to these constructs should be developed . Whilst attempts were made to amend the cause scale to enhance its applicability, further modifications may be needed to develop a more robust factor structure.

Correlations between IPQ-BCS subscales were consistent with theory and previous research and showed good construct validity. The original consequences scale correlated positively with the new tamoxifen consequences subscale, but the correlation was only moderate, which supports the idea that patients can differentiate symptoms from their breast cancer and

their tamoxifen treatment. Previous research in a cancer setting has found overlap of the consequences and emotional representations scales, where items from both subscales loaded onto the same factor (Giannousi et al., 2010). However, the IPQ-BCS correlations between these subscales were only moderate and the hypothesised factor structure was supported, suggesting that emotional representations around recurrence are distinct from consequences of breast cancer. The risk of recurrence scale, which was adapted from the previous timeline cyclical scale, showed that having high beliefs of a recurrence was associated with higher consequences, higher emotional representations and lower cure beliefs.

The personal and treatment control subscales were positively correlated, but the correlations were low enough to support the assumption of two distinct constructs, which is consistent with previous research (Dempster & McCorry, 2012; Giannousi et al., 2010; Moss-Morris et al., 2002). Women who scored highly on the two control subscales were less likely to believe they would have a recurrence, more likely to believe their breast cancer had been cured and more likely to have higher coherence beliefs. Women who attributed a high number of symptoms to tamoxifen were significantly more likely to believe they would have a risk of recurrence and less likely to believe they were cured, but these were small correlations. This is consistent with correlations found in previous research (Hagger & Orbell, 2003) and suggests that there is a relationship between symptom experience and perceptions of risk.

The correlations between IPQ-BCS subscales, HADS distress and BMQ treatment beliefs provided further support for construct validity. Higher concerns about tamoxifen were associated with higher tamoxifen consequences, a greater number of symptoms attributed to tamoxifen and to a lesser extent, higher breast cancer consequences. This is expected in this population as tamoxifen concerns focus almost exclusively on side effects (Moon, Moss-Morris, Hunter, & Hughes, 2016) and are therefore related to beliefs around consequences and symptom attribution. Understanding the interactions between illness perceptions and medication beliefs may help understand medication non-adherence in BCS (Horne & Weinman, 2002). HADS distress was associated with tamoxifen consequences, breast cancer consequences and emotional representations. These relationships make theoretical sense, as greater illness consequences are likely to contribute to levels of distress. However, as this was cross-sectional data, the direction of the effect cannot be established. It may be that women who experience higher levels of distress perceive greater consequences from their illness or ongoing treatment.

Strengths of this study include the large sample size and robust analysis. The scale was amended based on interviews with patients, and before being analysed, it was subject to think-aloud analysis. Furthermore, patients were recruited from hospitals throughout

England, which should enhance the generalisability of the results. However, there were several limitations. Firstly, participants from the same sample were used to develop the items on the questionnaire and to test the questionnaire in the think-aloud studies. Secondly, the factor structure has only been tested and validated in one sample. Future research could test whether the IPQ-BCS could be modified further for use in different cancer types with similar survivorship issues to BCS. Overall, results suggest that the modified IPQ-BCS is a valid and reliable measure. It is well understood in BCS and has a clear factor structure with 10 distinct constructs (cause, identity, cure, tamoxifen consequences, risk of recurrence, breast cancer consequences, personal control, treatment control, coherence and emotional representations). Utilising this scale will help us understand how women feel about their illness and their ongoing treatment as they move into survivorship. Illness perceptions have been shown to be relevant to many of the psychosocial issues inherent to BCS, such as fatigue, non-adherence, distress and FCR. Using the IPQ-BCS will allow researchers to see how dimensions such as emotional representations and sense of coherence affect illness behaviours such as adherence, or outcomes such as QOL and survival, and will help generate interventions to support these patients. Whilst the scale was developed for tamoxifen treatment, it is likely it will be equally as applicable for women who have been prescribed other hormonal therapy such as aromatase inhibitors. It can also be used in other areas, such as to investigate beliefs around cancer in relation to FCR, fatigue or distress.

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5.3. Summary

This paper reports on the modification of the IPQ-R for BCS. The scale is valid and reliable and can therefore be used to examine illness perceptions held in BCS in a range of contexts, including distress, fear of recurrence, quality of life, health behaviours and survival. Using the IPQ-BCS would overcome any limitations associated with using non-validated scales, or with using the generic IPQ-R to measure these constructs. In particular, the scale was developed to explore the relationship between illness perceptions and tamoxifen adherence in BCS. This analysis is presented in the following chapter.

6. More than just side effects: the role of clinical and psychological factors in non-adherence to tamoxifen

6.1. Chapter Overview

This chapter describes a large cross-sectional study to compare the Common Sense Model (CSM) and the Theory of Planned Behaviour (TPB) in explaining tamoxifen non-adherence. This study also forms the basis of the longitudinal study which is presented in Chapter 8. Women in the cross-sectional study who were in their first year of adjuvant treatment were followed up for one year.

The previous chapters have shown that there are few consistent predictors of tamoxifen non-adherence. Bringing the results of the qualitative study and systematic review together suggests that one of the key factors associated with non-adherence is how women weigh their side effects up against their beliefs about tamoxifen and about their breast cancer. However, so far, few modifiable factors have been identified. In order to improve understanding of psychosocial factors associated with non-adherence and to develop an intervention to improve adherence rates, there is a need to identify more modifiable factors. The previous studies have suggested several variables which may be important for tamoxifen non-adherence, including side effects, medication beliefs, social support and self-efficacy for medication taking. The cross-sectional study allows these variables to be tested in a large robust study using validated measures, and using models of health behaviour as a framework. This will help to provide clarity on the strength and direction of relationships, and will give much needed information for intervention development. Using a large quantitative design will also allow for elements from the CSM and TPB to be tested. Results will provide insight into which factors provide the best explanation of non-adherence, and will identify if either model provides superior explanation. If both models provide good prediction, then a more parsimonious model may be able to be created. This could reduce redundancy, aid with design of future studies and enhance the effectiveness of future interventions (Corda et al., 2010; Holmes et al., 2014; Michie et al., 2008).

6.2. Published paper

Article title: More than just side effects: the role of clinical and psychosocial factors in non-adherence to tamoxifen

Authors: Zoe Moon, Rona Moss-Morris, Myra S Hunter, Lyndsay D Hughes

Health Psychology Section, Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

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Keywords: adherence; breast cancer; tamoxifen; theory of planned behaviour; common sense model

Corresponding author:
Lyndsay D Hughes
Health Psychology Section,
Institute of Psychiatry, Psychology & Neuroscience,
5th Floor Bermondsey Wing, Guy's Hospital,
London SE1 9RT, UK
Email lyndsay.hughes@kcl.ac.uk

More than just side effects: the role of clinical and psychosocial factors in non-adherence to tamoxifen

Objectives: Tamoxifen non-adherence is apparent in up to half of breast cancer survivors and is associated with increased risk of recurrence and reduced quality of life. However, factors contributing to non-adherence in this population are currently poorly understood. This study explored the relationship between key components of the Common Sense Model of Illness Representations (CSM) / the Theory of Planned Behaviour (TPB) and intentional and unintentional non-adherence in a large sample of women prescribed tamoxifen following primary breast cancer.

Design: Cross-sectional questionnaire study (n=777).

Methods: Women were eligible if they were over 18, had been diagnosed with primary breast cancer and had been prescribed tamoxifen. Participants were recruited in clinic or online and completed questionnaires assessing illness perceptions, treatment beliefs, adherence, quality of life, social support, distress and the key TPB components. Logistic regressions were conducted to test elements from each model and to identify correlates of intentional and unintentional non-adherence.

Results: Patients were classified as non-adherent based on Medication Adherence Rating Scale scores. 44% of the population were non-adherent; 41% reported unintentional non-adherence and 9% reported intentional non-adherence. Study variables accounted for more variance in intentional (Nagelkerke R^2 = 46%) than unintentional non-adherence (Nagelkerke R^2=17%). Intentional non-adherence was best explained by a combination of TPB and CSM variables, but these variables did not contribute significantly to unintentional non-adherence.

Conclusions: The TPB and the CSM provide a useful framework for understanding intentional tamoxifen non-adherence. Elements from both models should be considered when designing interventions to increase adherence rates.

Introduction

Breast cancer is the most common cancer in women in the UK, and whilst survival rates are improving, it is still the second most common cause of cancer-related death in the UK (Cancer Research UK, 2014). About 75% of breast cancers are oestrogen receptor positive (ER+), which means the cancer cells are stimulated by oestrogen (Harrell et al., 2007). Adjuvant hormonal therapy (HT) such as tamoxifen is prescribed to women with ER+ breast cancer to reduce the risk of recurrence. Tamoxifen, which works by blocking the oestrogen receptor, reduces the risk of recurrence by 46% and the risk of mortality by 26% (Early Breast Cancer Trialists' Collaborative Group, 1998). It is prescribed for between five and ten years and is one of the most effective systemic therapies available for ER+ early breast cancer (Aguilar et al., 2010).

Treatment adherence, defined as the extent to which patients take their medication as prescribed (Sabate, 2003), is often not considered to be an issue with cancer patients, due to the life threatening nature of the illness (Wu, Stafkey-Mailey, & Bennett, 2012). However, despite the clear clinical benefits of tamoxifen, many patients either stop taking their medication early or do not take the full dosage. Non-adherence ranges from 6% - 55% (Ayres, Baldoni, Borges, & Leira Pereira, 2014; Hershman et al., 2011; McCowan, Wang, Thompson, Makubate, & Petrie, 2013) and rises over time (Hershman et al., 2010; Partridge, Wang, Winer, & Avorn, 2003). This variability in adherence rates is likely due to variations in study design and populations, such as different healthcare and cultural contexts. Furthermore, there is significant variability in the tools used to assess adherence, with studies utilizing self-report measures reporting higher rates of adherence (Moon et al., 2017). A further 50% of patients completely discontinue tamoxifen within five years (Kostev et al., 2013; van Herk-Sukel et al., 2010), which is known as non-persistence. Non-adherence and non-persistence to tamoxifen are associated with increased risk of death and early recurrence (Barron, Cahir, Sharp, & Bennett, 2013; Hershman et al., 2011; Makubate, Donnan, Dewar, Thompson, & McCowan, 2013), as well as fewer quality adjusted life years and increased medical costs (McCowan et al., 2013). This indicates a need to understand why women are not adhering, so we can intervene to increase adherence rates and improve clinical outcomes. Identifying psychosocial predictors of non-adherence is essential in the development of interventions, as these factors have the potential to be modified. For example, medication beliefs and perceived control over medication taking are associated with medication adherence in a range of conditions (Conner, Black & Stratton, 1998; Horne & Weinman, 1999) and have been successfully targeted in interventions (Petrie et al., 2012; Sheeran & Orbell, 2000). However, evidence on modifiable psychological predictors of tamoxifen adherence is currently lacking (Moon, Moss-Morris, Hunter, Carlisle, & Hughes, 2017;

Murphy, Bartholomew, Carpentier, Bluethmann, & Vernon, 2012), with an emphasis in the literature on non-modifiable clinical and demographic factors.

Non-adherence can be conceptualised as intentional, where the patient makes a deliberate decision not to adhere, or unintentional, where they may forget or not understand the instructions. Unintentional non-adherence is more prevalent in breast cancer, however this may be due to forgetting being more socially acceptable and therefore more frequently reported (Atkins & Fallowfield, 2006; Unni & Farris, 2011). Some studies suggest that unintentional non-adherence may be related to medication beliefs (Gadkari & McHorney, 2012; Schüz et al., 2011), which questions how unintentional these behaviours are. However, recent studies in breast cancer have supported the idea of a distinction between unintentional and intentional non-adherence (Kimmick et al., 2015; Wouters et al., 2014). Understanding these different types of non-adherence and the associated predictors would be useful in tailoring interventions to improve adherence.

Tamoxifen is associated with side-effects, including hot flushes, vaginal dryness and low mood, which are often assumed to drive non-adherence. However, the relationship between side-effects and non-adherence is inconsistent (Moon et al., 2017). Whilst a recent systematic review has found some evidence for potentially modifiable psychosocial correlates of HT non-adherence, including self-efficacy for medication taking, medication beliefs and social support (Moon et al., 2017), previous research has largely failed to use theoretical models when investigating non-adherence. Theory provides a structured framework for investigating key determinants of non-adherence and helps with intervention development (Holmes, Hughes, & Morrison, 2014). This study will use two popular models of health behaviour to investigate tamoxifen non-adherence; the Common Sense Model (CSM) and the Theory of Planned Behaviour (TPB). These models have been used extensively to predict health behaviours, but to the best of our knowledge, no peer reviewed research has applied them to tamoxifen adherence.

The TPB proposes that adherence is driven by intentions to engage with treatment, which are in turn influenced by subjective norms, attitudes and perceived behavioural control (PBC), which also exerts a direct influence over behaviour (Ajzen, 1991). Previous studies have supported the TPB as a framework for understanding non-adherence (Kagee & Van der Merwe, 2006) with key TPB variables explaining large proportions of variance in medication adherence (Bane, Hughe, & McElnay, 2010; Conner et al., 1998). The CSM proposes that patients hold illness representations, or implicit common sense beliefs about their illness, which are used as a framework for making sense of and coping with an illness (Leventhal, Diefenbach, & Leventhal, 1992). Key illness perceptions are identity (the label

given to the illness and symptoms experienced), causal beliefs, timeline beliefs, treatment control, personal control and consequences. Patients also hold emotional representations of their illness. These illness perceptions have been associated with adherence in several studies, highlighting the utility of the CSM as a framework for investigating non-adherence (Brewer, Chapman, Brownlee, & Leventhal, 2002; Patel & Taylor, 2002; Ross, Walker, & MacLeod, 2004). The CSM is a dynamic model where illness perceptions affect selection of coping strategies, and the outcome of these coping strategies affects illness perceptions. The explanatory power of the CSM has been improved by the addition of medication beliefs, which may act as a more proximal determinant of non-adherence. These medication beliefs include concerns, and necessity beliefs, which relate to how necessary the patient feels the medication is for their current and future health. Necessity and concern beliefs are stronger predictors of adherence than clinical or demographic factors (Horne & Weinman, 1999). The differential between necessity and concern beliefs is often used to predict non-adherence and represents a cost-benefit analysis patients may undergo before making decisions about treatment (Horne & Weinman, 1999; Wileman et al., 2011). This framework also includes more general beliefs about medication, but the specific beliefs (necessity/concerns) have been shown to be more important in relation to medication adherence (Grunfeld et al., 2005; Horne & Weinman, 1999; Zwikker et al., 2014a).

The primary aim of this study was to explore the relationship between key aspects of the CSM and TPB and both intentional and unintentional non-adherence, in order to facilitate the development of interventions to improve adherence. Elements from both models were included to heighten the explanatory power and to explore both perceptions around cancer survivorship (CSM) and the medication taking behaviour itself (TPB), as it was felt that both these sets of variables may have an influence on non-adherence. Testing both models concurrently allows for a broader range of predictor variables to be tested, and may allow for creation of a more parsiminous model. Demographic, clinical and other psychosocial variables such as distress and social support were controlled for in the analysis as they have previously shown associations with tamoxifen non-adherence (Moon et al., 2017). Based on previous research, we hypothesise that unintentional non-adherence will be reported more frequently than intentional non-adherence, and that psychological variables from the CSM andTPB, such as necessity and concern beliefs, will be related more to intentional than unintentional non-adherence.

As adherence rates fall across time (Nekhlyudov, Li, Ross-Degnan, & Wagner; Schover, Baum, Fuson, Brewster, & Melhem-Bertrandt, 2014), a secondary aim was to investigate whether adherence was higher in women who were nearer the beginning of treatment. Differences in CSM and TPB variables between women within six months of treatment and

women who are later on in treatment were also explored, to provide understanding of how illness or treatment beliefs differ across the treatment trajectory. Little is currently known about the illness beliefs held by these patients or how they may change over time.

Method

Participants and procedure

The study was approved by the Northampton National Research Ethics Committee (REF 14/EM/1207). Women were eligible for the study if they were over 18, had been diagnosed with primary breast cancer and had been prescribed tamoxifen. Patients were recruited through 27 oncology clinics across England and through online advertisements. In clinic, eligible women were identified by clinic staff and were told about the research during their appointment. Patients were given an information sheet and consent form as well as verbal information about the study. They could complete the questionnaire in clinic, take it away and return it using a stamped addressed envelope, or complete it online. Informed consent was taken from all participants. Some patients were recruited through a postal invitation sent out by clinic staff to eligible patients. Online advertisements were placed on patient support websites and Facebook groups. When a participant saw this advertisement, they contacted the researcher who gave them information about the study and screened them for eligibility. They were then either posted the questionnaire or given a link to complete it online. The questionnaire took between 20 – 30 minutes to complete.

Measures

Sociodemographic and clinical variables

Participants provided data on demographic (age, ethnicity, relationship status, employment status, age left full time education, menopausal status at diagnosis), clinical (breast cancer stage, previous treatment, comorbidities) and treatment related factors (date prescribed tamoxifen, duration of tamoxifen treatment, type of prescribing clinician).

Social Support

Social support was measured using the Multidimensional Scale of Perceived Social Support (Zimet, Dahlem, Zimet, & Farley, 1988). Each item was scored on a seven point scale, with higher scores indicating higher levels of support. The scale has demonstrated good internal and test-retest reliability and has been used successfully to measure social support in patients with breast cancer (Oztunc, Yesil, Paydas, & Erdogan, 2013). Internal consistency in the current study was 0.96.

Distress

Distress, measured using The Hospital Anxiety and Depression Scale (HADS), was included as a covariate (Zigmond & Snaith, 1983). The scale includes seven items measuring depression and seven measuring anxiety. Following recent recommendations, the scale was used as a measure of general distress (Norton, Cosco, Doyle, Done, & Sacker, 2013). The scale showed good reliabity in the current study (α=.91).

Side effects

The FACT-ES is a quality of life scale for patients with breast cancer taking HT (Fallowfield, Leaity, Howell, Benson, & Cella, 1999). The additional concerns subscale was used to measure side-effects. Patients provide an answer on a five point scale from 'not at all' to 'very much' to indicate how much they have experienced each side-effect for a list of 18 side effects. This provides a combined measure of both number and intensity of side-effects, representing the overall level of bother from side effects. The subscale showed good reliability in the current study (α =.87).

Information about treatment

To assess how informed patients are about their treatment, they were asked the extent to which they agreed or disagreed with four statements, such as "I feel confident in my understanding of how tamoxifen helps me". The scale showed good reliability (α =.89) in the current study.

Illness representations

The IPQ-BCS (Moon, Moss-Morris, Hunter, & Hughes, 2017), a modified version of the Revised Illness Perceptions Questionnaire, was used to measure components of the CSM. The scale has good psychometric properties and includes ten subscales; cure, risk of recurrence, tamoxifen consequences, breast cancer consequences, personal control, treatment control, illness coherence, emotional representations, tamoxifen identity and causes of recurrence. The subscales have previously demonstrated good internal reliability with Cronbach's alphas ranging from .76 to .92. Each scale includes four items scored on a 5-point Likert-type scale, with the exception of the tamoxifen identity and causes of recurrence scales. The identity scale includes a list of symptoms where participants indicate if they have experienced each symptom and if they attribute it to their tamoxifen treatment. The scale is scored by summing the number of symptoms attributed to tamoxifen. The causes of recurrence scale includes 14 possible causes. A previous exploratory factor analysis has indicated two factors for causes; psychological attributions (e.g. *my emotional state*) and health behaviours (e.g. *diet or eating habits)* (Moon et al., 2017).

Beliefs about Medicines

Beliefs about Medicines were measured as part of the extended CSM, which has particular relevance for medication adherence. The BMQ-Specific was used to measure beliefs regarding the necessity of taking tamoxifen and concerns about adverse effects. The scale has previously shown good psychometric properties (Horne, Weinman, & Hankins, 1999). A differential score was calculated by taking the total score for concerns away from the total score for necessity beliefs, as recommended by the authors of the BMQ (Horne & Weinman, 1999). A positive differential suggests that the necessity beliefs outweigh the concerns.

Theory of Planned Behaviour

Items relating to TPB variables were developed following guidelines from Francis et al. (2004) and Ajzen (2002). Subscales include intention to take tamoxifen, subjective norms, attitude and PBC. Intention, subjective norm and PBC were measured on a 7-point Likert scale. Attitudes were measured with five semantic differential scales scored on a ten point scale. Each subscale showed good reliability in the current study ($\alpha = 0.67 – 0.82$), with the exception of subjective norms ($\alpha = 0.52$), however all subscales were included in order to fully test the model.

Adherence

The Medication Adherence Report Scale (MARS; Horne, Hankins, & Jenkins, 2001) includes five statements about taking medication, which are each scored on a five point scale from never to always. The scale attempts to avoid any issues regarding social desirability by asking questions in a non-threatening and non-judgemental way. The scale has demonstrated good internal reliability and test-retest reliability and has been used multiple times in breast cancer patients (Boonstra et al., 2013). Scores on the MARS were strongly positively skewed and therefore the data was dichotomised based on recommendations from previous papers (de Vries et al., 2014). The MARS includes a one item sub-scale on unintentional non-adherence (total score of 5) and a four item sub-scale on intentional non-adherence (total score of 20), with a total possible overall adherence score of 25. On the basis of previous studies, participants were classed as unintentionally non-adherent if they scored below 5 and intentionally non-adherent if they scored below 20 on the respective sub-scales (Daleboudt et al., 2011; Timmers et al., 2014; de Vries et al., 2014). Participants could be classed as both intentionally and unintentionally non-adherent.

Statistical analysis

Relationships between hypothesized correlates and intentional/unintentional non-adherence were tested using Cramer's V for categorical variables and biserial correlations for continuous variables. Separate multiple logistic regressions were carried out to assess the relationships between intentional and unintentional non-adherence and components of the CSM and TPB. Clinical, demographic and potentially confounding psychosocial variables which showed a significant bivariate relationship with non-adherence were entered into the first step of the regression models. The CSM and TPB components were entered into the next step, to assess their impact on adherence after the demographic variables have been taken into account. The ability of components from each model to explain non-adherence was assessed using Nagelkerke R^2 (pseudo R^2) to measure the proportion of variance explained. Model fit was also assessed by the -2 Log Liklihood statistic (-2LL). Lower -2LL values indicate superior model fit, and therefore if the addition of variables reduces the -2LL value, the variables have improved the model fit. The reduction in the -2LL statistic for each step is represented by chi-squared. T-tests using Bonferroni correction were used to compare women in their first year of treatment to women who were later on in treatment.

Results

Demographics of sample

1246 women were invited to participate from clinics and 758 women completed the questionnaire (61% response rate). An additional 60 women were recruited through online advertising. Forty-one (5%) women reported having discontinued tamoxifen and were removed from the sample. The final sample included 777 women. All participants were female, had Stage I-III breast cancer and had been prescribed tamoxifen (Table 1). The mean age was 53 (SD=10, range 30-90). Participants were mostly White British (86%), married (58%) and employed (65%). Just under half of patients had been prescribed tamoxifen less than one year ago, 22% 1-2 years ago and 31% over two years ago. Two thirds of participants self-reported being premenopausal or menopausal at time of diagnosis.

Adherence rates

Non-adherence was rated using cut-offs on the MARS. 44% (n=340) showed any sign of non-adherence, 9% (n=71) reported intentional non-adherence and 41% (n=321) reported unintentional non-adherence.

Explanatory variables

Means and SDs for each subscale are shown in Table 2. Mean anxiety levels (6.9, SD=4.4) were higher than depression rates (4.1, SD=3.8) but both were within normal ranges for the general population. The mean distress score was 11.0 (SD=7.5). Participants had relatively high beliefs in treatment control (mean=15.3, SD=2.5), illness coherence (mean=15.4, SD=2.9) and cure (mean=15.7, SD=3.0). An average of 5.6 symptoms were attributed to tamoxifen (SD=4.9). BMQ differentials were slightly above 0, showing that on average, participants had positive necessity-concern differentials (2.1, SD=5.2). Mean scores for intentions (6.5, SD=1.2), subjective norm (6.0, SD=1.0) and PBC (6.2, SD=1.0) were all high and attitudes were positive (7.9, SD=1.7).

Intentional non-adherence

The only demographic or clinical variables associated with intentional non-adherence were previously having a double mastectomy (Cramer's V=.10, p=.01) and months since prescribed tamoxifen (r_b=.17, p=.01) (See supplementary material, Appendix E). Side-effect intensity (r_b=.44, p<.001), distress (r_b=.37, p<.001), social support (r_b =-.19, p=.013) and how informed participants were (r_b=-.13, p=.030) were also associated with intentional non-adherence and were entered into the first step of the model.

Table 1. Participant demographics.

Characteristic	N (%)
Age	30 – 90 Mean: 53 (SD: 10)
Ethnicity	666 (86%) White British
	110 (14%) Other
Relationship status	555 (72%) With partner
	218 (28%) Separated /Divorced /Single/Widowed
Job status	504 (65%) Employed full time / part time
	209 (28%) Retired / Homemaker / Other
	61 (8%) Unemployed
Time since prescribed tamoxifen	< 6 months: 206 (28%)
	6 – 12 months: 142 (19%)
	1 – 2 years: 162 (22%)
	2 – 3 years: 99 (13%)
	3 – 4 years: 61 (8%)
	>4 years: 75 (10%)
Stage at diagnosis	Stage I: 308 (40%)
	Stage II: 326 (43%)
	Stage III: 93 (12%)
	Unsure: 35 (5%)
	Missing: 14 (2%)
Menopausal status at diagnosis	Pre-menopausal/menopausal: 511 (67%)
	Post-menopausal: 212 (28%)
	Unsure: 35 (5%)
	Missing: 18 (2%)
Previous treatment	Lumpectomy: 63%
	Single Mastectomy: 34%
	Double Mastectomy: 6%
	Chemotherapy: 51%
	Radiotherapy: 73%
Tamoxifen duration	One or two years: 16 (2%)
	Five years: 496 (64%)
	Ten years: 190 (25%)
	For life: 1 (0.1%)
	Unsure: 40 (5%)
	Missing: 26 (3%)
Healthcare professional who prescribed tamoxifen	Oncologist: 595 (77%)
	Surgeon: 130 (17%)
	Nurse: 24 (3%)
	GP: 5 (1%)
	Unsure / missing: 23 (2%)

Table 2. Relationship between explanatory variables and non-adherence

	Mean (SD)	Range	Correlation with intentional non-adherence	Correlation with unintentional non-adherence
Necessity/concerns differential	2.10 (5.23)	-20 - 20	-0.44***	-0.18***
Tamoxifen consequences	10.06 (4.09)	4 – 20	0.49***	0.12**
Breast cancer consequences	12.11 (3.71)	4 – 20	0.21***	0.07
Risk of recurrence	10.48 (3.45)	4 – 20	0.00	0.04
Cure	15.66 (3.04)	4 – 20	-0.08	0.04
Personal control	13.73 (3.01)	4 - 20	-0.07	0.09
Treatment control	15.32 (2.46)	6 - 20	-0.09	0.02
Coherence	15.38 (2.86)	4 - 20	-0.06	0.01
Emotional representations	13.23 (4.30)	4 - 20	0.08	0.07
Attributing side effects to tamoxifen	5.75 (4.87)	0 – 22	0.38***	0.19***
Cause: psychological attributions	9.52 (2.87)	3 - 15	0.23***	0.09
Cause: health factors	13.15 (2.99)	4 - 20	-0.03	0.10*
Attitude	7.86 (1.66)	1 – 10	-0.35***	0.14**
Intention	6.46 (1.18)	1 -7	-0.69***	0.22***
Subjective norm	6.03 (1.03)	1 – 7	-0.19**	0.14**
Perceived behavioural control	6.18 (1.02)	1-7	-0.70***	0.22***

*** p≤.001, **p<.01, *p<.05

CSM components associated with intentional non-adherence in the bivariate analysis were; BMQ differential, tamoxifen consequences, breast cancer consequences, cause: psychological attributions and tamoxifen identity. From the TPB; intention, subjective norm and attitude were all associated with intentional non-adherence (Table 2). Two logistic regressions were conducted to test separately the measured components of the CSM and TPB and a third regression combined the CSM and TPB variables. The model combining both the CSM and TPB variables explained the most variance in intentional non-adherence (Nagelkerke R^2=46%) (Table 3). In this model, the variables in Step 1 explained 20% of the variance ($\chi^2(5) = 60.06$, p<.001, R^2=20%). Higher levels of distress (OR=1.06, 95% CI=1.02-1.11) and higher intensity of side-effects (OR=1.05, 95% CI=1.03-1.08), having a double mastectomy (OR=3.18, 95% CI=1.33-7.60) and a longer duration of tamoxifen prescription (OR=1.01, 95% CI=1.00-1.02) were associated with increased odds of intentional non-adherence.

Table 3. Multiple logistic regressions to predict intentional non-adherence

	CSM (n=658)		TPB (n=652)		Combined model (n=611)	
	OR	95% CI	OR	95% CI	OR	95% CI
Step 1						
Side effect intensity	1.02	0.99 – 1.05	1.03	1.00 – 1.06	1.01	0.98 – 1.05
Social support	0.99	0.76 – 1.28	1.01	0.77 – 1.31	0.94	0.70 – 1.26
Extent patients feel informed about tamoxifen	0.95	0.87 – 1.05	1.01	0.91 – 1.11	1.03	0.91 – 1.15
Distress	1.04	0.99 – 1.09	1.03	0.98 – 1.09	1.05	0.99 – 1.12
Months since prescribed	1.01	0.99 – 1.03	1.01	0.99 – 1.02	1.01	0.99 – 1.03
Double Mastectomy (received)	3.55	1.37 – 9.18	5.35	2.07 – 13.88	6.41	2.26 – 18.19
Step 2						
Necessity/concerns differential	0.89	0.83 – 0.95			0.97	0.89 – 1.06
Tamoxifen consequences	1.15	1.04 – 1.27			1.06	0.94 – 1.19
Breast cancer consequences	0.96	0.87 – 1.08			0.93	0.81 – 1.05
Risk of recurrence	0.88	0.80 – 0.97			0.87	0.76 – 0.98
Cure	0.94	0.84 – 1.06			0.96	0.84 – 1.10
Personal control	0.93	0.81 – 1.05			0.97	0.85 – 1.12
Treatment control	1.10	0.92 – 1.23			1.05	0.86 – 1.28
Coherence	1.02	0.91 – 1.17			1.01	0.87 – 1.16
Emotional representations	0.93	0.86 – 1.03			0.96	0.86 – 1.07
Attribution of symptoms to tamoxifen	1.03	0.95 – 1.09			1.05	0.96 – 1.14
Cause: psychological attributions	2.06	1.34 – 3.05			2.28	1.40 – 3.71
Cause: health behaviours	0.58	0.40 – 1.01			0.41	0.24 – 0.72
Attitude			1.15	0.90 – 1.47	1.29	0.98 – 1.70
Intention			0.69	0.53 – 0.89	0.72	0.53 – 0.98
Subjective norm			1.19	0.86 – 1.63	1.11	0.78 – 1.58
Perceived behavioural control			0.43	0.30 – 0.62	0.37	0.24 – 0.56
	Step 1 -2LL: 353.3 Step 1 R^2 = .19 Step 1 $\chi2$ = 62.1 (p<.001) Step 2 –2LL: 302.79 Step 2 R^2 = .34 Step 2 $\Delta\chi2$ (12) = 50.52 (p<.001)		Step 2 –2LL: 279.9 Step 2 R^2 = .39 Step 2 $\Delta\chi2$ (4) = 64.4 (p=.000)		Step 1 -2LL: 332.3 Step 1 R^2 = .20 Step 1 $\chi2$ =60.06 (p<.001) Step 2 –2LL: 243.1 Step 2 R^2 = .46 Step 2 $\Delta\chi2$ (16) = 89.4 (p=.000)	

Adding the CSM and TPB variables significantly improved the model fit and explained a further 26% of the variance ($\Delta\chi^2(16) = 89.4$, p<.001, R^2=46%). After adding these variables, the only variable in step 1 still significantly associated with non-adherence was double mastectomy (OR=6.41, 95% CI=2.26-18.20). In terms of CSM variables, stronger beliefs in

the risk of recurrence (OR=0.87,95% CI=0.76-0.98) and stronger beliefs that health behaviours cause a recurrence were associated with decreased odds of non-adherence (OR=0.41, 95% CI=0.24-0.72), whereas beliefs that stress caused a recurrence were associated with two-fold increased odds of non-adherence (OR=2.28, 95% CI =1.40 – 3.71). Higher levels of PBC (OR=0.37, 95% CI=0.24-0.56) and intention (OR=0.73, 95% CI=0.52-0.98) were associated with decreased odds of intentional non-adherence.

Unintentional non-adherence

Individual associations between adherence and variables were tested using Cramer's *V* and biserial correlations. There were small but significant relationships between unintentional non-adherence and ethnicity (Cramer's V =.09, p=.007), relationship status (Cramer's V=.13, p=.007) and menopausal status (Cramer's V=.15, p =.001). There was a moderate relationship between job status and unintentional non-adherence (Cramer's V=.22, p<.001) and a weak relationship between previous chemotherapy and unintentional non-adherence (Cramer's V=.08, p=.038) (See supplementary material). Age (r_b=.22, p<.001), age left full time education (r_b=.12, p=.006), side-effect intensity (r_b=.14, p<.001), social support (r_b=-.14, p=.007) and months since prescribed (r_b=.21, p<.001) were correlated with unintentional non-adherence. In terms of variables from the CSM, unintentional non-adherence was associated with; necessity/concerns differential, tamoxifen consequences, tamoxifen identity and cause: health behaviours. TPB variables associated with unintentional non-adherence in the bivariate analysis were PBC, intention, subjective norm and attitudes (Table 2). Separate logistic regressions were carried out to test the measured components of the CSM, the TPB and then a combination of CSM and TPB variables. The model including the CSM variables and the model including a combination of CSM and TPB variables both explained 17% of the variance in unintentional non-adherence (Table 4). Control variables were entered in step one, explaining 13% of the variance in unintentional non-adherence ($\Delta\chi^2(10) = 53.1$, p<.001, R^2=13%). Women who were white (OR=0.48, 95% CI=0.24-0.99) or older (OR=0.97, 95% CI=0.94-0.99) had lower odds of non- adherence and women who were employed (OR=2.08, 95% CI=1.32-3.30) or had been taking tamoxifen longer (OR=1.02, 95% CI=1.01-1.03) had higher odds of non-adherence. Adding variables from the CSM/TPB in the second step of the model explained a further 4% of variance, but did not significantly improve the model fit.

Table 4. Multiple logistic regressions to predict unintentional non-adherence

	CSM (n=575)		TPB (n=574)		Combined model (n=535)	
	OR	95% CI	OR	95% CI	OR	95% CI
Step 1						
Side effect intensity	1.01	0.99-1.03	1.01	0.99-1.02	1.00	0.98-1.03
Social support	0.88	0.75-1.02	0.91	0.79-1.06	0.89	0.76-1.03
Ethnicity (white)	0.43	0.21-0.88	0.53	0.26-1.07	0.43	0.20-0.91
Age	0.96	0.93-0.99	0.97	0.95-1.00	0.97	0.94-1.00
Relationship status (with partner)	0.73	0.47-1.11	0.77	0.51-1.17	0.74	0.48-1.16
Employment status (employed)	2.16	1.37-3.38	2.12	1.95-3.33	2.10	1.30-3.39
Months since prescribed	1.02	1.01-1.03	1.02	1.01-1.03	1.02	1.01-1.03
Chemotherapy (received)	0.99	0.66-1.50	0.93	0.63-1.39	1.01	0.66-1.54
Age left full time education	0.99	0.93-1.05	1.02	0.96-1.08	0.98	0.92-1.05
Menopausal status (premenopausal)	0.66	0.40-7.09	0.83	0.51-1.34	0.69	0.38-1.10
Step 2						
Necessity/concerns differential	0.96	0.93-1.00			0.97	0.93-1.02
Tamoxifen consequences	1.00	0.94-1.07			0.98	0.92-1.05
Breast cancer consequences	0.98	0.92-1.05			0.97	0.91-1.04
Risk of recurrence	0.98	0.92-1.05			0.98	0.91-1.05
Cure	1.01	0.95-1.09			1.03	0.96-1.11
Personal control	1.01	0.93-1.10			1.03	0.95-1.12
Treatment control	1.04	0.94-1.16			1.03	0.92-1.15
Coherence	1.02	0.94-1.09			1.04	0.96-1.12
Emotional representations	1.01	0.96-1.07			1.02	0.96-1.08
Symptoms attributed to tamoxifen	1.03	0.98-1.08			1.03	0.98-1.09
Cause: psychological stress	1.04	0.82-1.31			1.08	0.85-1.38
Cause: health behaviours	1.21	0.89-1.63			1.07	0.78-1.46
Attitude			0.95	0.84-1.08	0.96	0.84-1.10
Intention			1.01	0.82-1.25	1.03	0.82-1.28
Subjective norm			0.95	0.79-1.15	0.99	0.80-1.21
Perceived behavioural control			0.80	0.63-1.02	0.78	0.60-1.01
	Step 1 -2LL: 719.4 Step 1 R^2 = .15 Step 1 $\chi 2$ (10) = 65.65 (p<.001)		Step 1 -2LL: 729.0 Step 1 R^2 = .13 Step 1 $\chi 2$ (10) = 56.1 (p<.001)		Step 1 -2LL: 680.1 Step 1 R^2 = .13 Step 1 $\chi 2$ (10) = 53.1 (p<.001)	
	Step 2 –2LL: 706.9 Step 2 R^2 = .17 Step 2 $\Delta\chi 2$ (12) = 12.5 (p=.405)		Step 2 –2LL: 721.4 Step 2 R^2 = .14 Step 2 $\Delta\chi 2$ (4) = 7.6 (p=.108)		Step 2 –2LL: 662.3 Step 2 R^2 = .17 Step 2 $\Delta\chi 2$ (16) = 17.9 (p=.331)	

Adherence rates and perceptions in newly prescribed patients

Compared to women not in their first six months since prescription, women in their first six months of tamoxifen prescription reported lower levels of distress (t(427)=-3.04, p=.003) and less intense side-effects (t(427) = -6.76, p=<.001) (Table 5). They also had higher intentions to take tamoxifen (t(627)=2.36, p=.003) and a more favourable attitude towards tamoxifen (t(663)=2.20, p=.028). With regards to illness/treatment beliefs, women within six months of prescription had lower scores on tamoxifen consequences (t(743) = -4.33, p=<.001), attributed fewer symptoms to tamoxifen (t(489)= 5.94, p=<.001) and were less likely to believe they were cured (t(316) = -3.36, p=.001). Women in their first six months of treatment also had significantly higher overall adherence rates (t(743) =-2.33, p=.020). However, adherence scores and attitudes were no longer significantly different after Bonferroni correction.

Table 5. Descriptive statistics and t-tests to compare women in their first six months of treatment to women later on in treatment

	Women in their first six months of treatment (n=206) (range 1 – 6 months) *Mean (SD)*	Women not in their first six months of treatment (n=539) (range 6 months – 8 years) *Mean (SD)*	p value
MARS scores	24.34 (1.44)	24.01 (1.76)	.020
Necessity/concerns differential	2.50 (5.36)	1.98 (5.24)	.233
Tamoxifen consequences	9.09 (3.56)	10.45 (4.26)	<.001*
Breast cancer consequences	12.33 (3.59)	12.03 (3.80)	.338
Risk of recurrence	10.41 (3.41)	10.52 (3.51)	.703
Cure	15.01 (3.41)	15.92 (2.84)	.001*
Personal control	13.59 (3.16)	13.82 (2.98)	.366
Treatment control	15.41 (2.49)	15.34 (2.42)	.722
Coherence	15.14 (2.98)	15.53 (2.78)	.099
Emotional representations	13.27 (4.20)	13.28 (4.33)	.982
Attributing side effects to tamoxifen	4.36 (3.79)	6.41 (5.09)	<.001*
Attitude	8.09 (1.45)	7.78 (1.71)	.028
Intention	6.63 (0.75)	6.41 (1.28)	.003*
Subjective norm	6.12 (0.98)	5.98 (1.04)	.097
Perceived behavioural control	6.28 (0.90)	6.14 (1.07)	0.73
Distress	23.73 (6.70)	25.48 (7.78)	.003*
Side effect intensity	35.11 (11.23)	41.62 (13.03)	<.001*

* Relationship remained significant after Bonferroni correction.

Discussion

This study explored associations between key components of the CSM and TPB with intentional and unintentional tamoxifen non-adherence. This is one of the largest studies to date to investigate psychosocial correlates of tamoxifen non-adherence and to use validated models of health behaviour as a framework. Results showed that key elements from both theories provide a useful framework for investigating intentional non-adherence. Drawing key variables from both the CSM and TPB provided the best explanation of intentional non-adherence, but these variables were not able to improve the explanation of unintentional non-adherence over and above clinical and demographic factors. Just under half of the sample were found to be non-adherent, with much higher percentages for unintentional than intentional non-adherence, as hypothesised. The figure of around 44% non-adherence has been found in many other studies of HT non-adherence (Kimmick, Camacho, Hwang, & Anderson, 2009; Lee et al., 2014; Seneviratne et al., 2015). Other studies have also supported the finding of higher rates of unintentional rather than intentional non-adherence (Kimmick et al., 2015; Tinari et al., 2015; Wouters et al., 2014). However, it is currently unclear if this reflects truly higher rates or the fact that forgetting may be more socially acceptable and is therefore endorsed more frequently by respondents (Atkins & Fallowfield, 2006). The current study identified unique correlates of intentional and unintentional non-adherence, and found poor prediction of unintentional non-adherence by psychological models. This suggests that these two types of non-adherence may be distinct from each other, and that participants are not simply reporting unintentional non-adherence as it is more socially acceptable.

The model combining both CSM and TPB variables provided the best fit for intentional non-adherence, explaining 46% of the variance. This combined model has been useful previously in predicting other health behaviours such as help seeking for breast symptoms (Hunter, Grunfeld, & Ramirez, 2003) and cervical cancer screening (Orbell, Hagger, Brown, & Tidy, 2006). Conceptualising these sets of beliefs together provides the best understanding of intentional non-adherence and is likely to be the best way to improve adherence. The results suggest that attitudes and perceptions around medication taking, as assessed by the TPB, and perceptions of breast cancer survivorship, as assessed by the CSM, are both central to understanding medication adherence. This highlights the importance of illness perceptions in breast cancer survivors and builds upon previous research using the CSM. Whilst women are no longer currently ill, their illness perceptions around survivorship and previous treatment are related to adherence. A recent review has found some evidence that interventions based on the CSM can improve adherence to a range of health behaviours,

but concluded that more research was needed (Jones, Smith, & Llewellyn, 2015). Whilst intentional non-adherence is reported less often than unintentional non-adherence, this behaviour is likely to be harder to modify and it is therefore of great interest that the CSM/TPB provide good explanation of this behaviour. Intentional non-adherence is also more likely to lead to discontinuation and therefore has strong clinical implications.

High risk of recurrence beliefs were associated with decreased odds of intentional non-adherence, probably because the fear of recurrence keeps women motivated to take tamoxifen. Stronger beliefs that psychological stress would cause a recurrence were associated with increased odds of non-adherence. If women endorse stress as a cause of recurrence then they may feel that there is no benefit in taking tamoxifen, as it does not control their stress levels. The necessity/concerns differential and tamoxifen consequences were significantly related to intentional non-adherence in the CSM model. This supports previous research suggesting that how people weigh up the necessity and concerns of treatment are related to whether or not they adhere (Horne & Weinman, 1999; Wileman et al., 2011). However the necessity/concerns differential and tamoxifen consequences were not significant once TPB variables were added, suggesting they may share variance with intention or PBC. Higher levels of PBC and intention were associated with decreased odds of intentional non-adherence. This is consistent with previous studies and theory (Bane et al., 2010) and suggests that interventions to improve PBC may help to improve adherence in this population. For example, implementation intentions, which are if-then goal plans where patients specify "I intend to do X at time Y in location Z", have been effective at increasing cervical cancer screening uptake (Sheeran & Orbell, 2000) and improving adherence in stroke survivors (O'Carroll, Chambers, Dennis, Sudlow, & Johnston, 2013).

Side-effects and distress were related to increased intentional non-adherence, but not when controlling for CSM and TPB variables. This is consistent with previous research which has found inconclusive evidence for the relationship between side-effects and non-adherence (Moon et al., 2017). Evidence suggests that women weigh up their necessity beliefs against their concerns when making decisions about taking tamoxifen (Fink, Gurwitz, Rakowski, Guadagnoli, & Silliman, 2004). If women have strong beliefs in the necessity of tamoxifen, they may continue to take it, regardless of side-effects. The results from the current study support this by showing that illness or treatment beliefs are stronger correlates of non-adherence than side-effects alone. This highlights the need to modify these psychological factors alongside side-effect management.

Women who had a double mastectomy were six times more likely to be intentionally non-adherent than women who did not have a double mastectomy, even after controlling for psychological variables. This may reflect a decision made by patients where they feel that tamoxifen is less necessary for them after removal of all breast tissue. A woman's choice to undergo a double mastectomy is a complex decision and is associated with a range of factors, such as treatment concerns (Molenaar et al., 2014) and fear of cancer recurrence (Nold et al., 2000). Therefore the relationship between non-adherence and receipt of double mastectomy may also be driven by one of these factors.

The fact that the majority of clinical and demographic variables were not related to intentional non-adherence supports the findings of a recent review showing few consistent clinical or demographic predictors of non-adherence (Moon et al., 2017). This lack of clear factors on which to screen patients for non-adherence highlights the importance of investigating psychological factors as potential avenues for intervention. Results from this study suggest that utilising the key variables drawn from the models concurrently will give researchers and practitioners the best chance at improving adherence rates. Non-adherence appears to be related to perceptions around cancer as well as perceptions of control over medication taking. Therefore interventions which focus solely on one of these factors may miss out on key predictors of non-adherence.

However, whilst these psychological models provided good explanation for intentional non-adherence, adding CSM and TPB variables did not improve the prediction of unintentional non-adherence. Furthermore, study variables were only able to explain 17% of the variance in unintentional non-adherence, compared to 46% for intentional non-adherence. Therefore, more research is needed to improve understanding of unintentional non-adherence to tamoxifen. Some interventions have shown success at improving adherence using reminders or action plans (Brown, Sheeran & Reuber, 2009; O'Carroll et al., 2013; Webb & Sheeran, 2006), but as yet, no studies have attempted to improve unintentional non-adherence in women taking tamoxifen.

Whilst there were small correlations between medication beliefs and unintentional non-adherence, these relationships were not maintained in the regression analysis. This contrasts with previous research showing that unintentional non-adherence is predicted by medication beliefs (Gadkari & McHorney, 2012; Schüz et al., 2011). However, a recent study found that medication beliefs were associated with intentional but not unintentional non-adherence to HT (Brett et al., 2016), supporting the results of the current study. This

suggests that unintentional non-adherence in this population may be influenced slightly by a patient's medication beliefs, but is much more likely to be due to forgetting or not establishing a good medication taking routine. This is further supported by the identification of unique predictors of both intentional and unintentional non-adherence.

Unintentional non-adherence was associated with demographic and clinical variables. Women who were white were less likely to be non-adherent than women who were not white, however the proportion of women of other ethnicities was small. Women who were older had higher odds of adherence, which has also been found in previous studies (Brett et al., 2016; Jacob Arriola et al., 2014; Kimmick et al., 2015) and may reflect the fact that young women may have difficulties setting a routine around work or raising a family. Women who were employed had higher odds of non-adherence, independent of the effects of age. This supports findings of recent studies in HT adherence (Brett et al., 2016; Quinn, Fleming, & O'Sullivan, 2016) and may be due to practical problems, such as experience of side-effects in the workplace. Women with a longer time since tamoxifen initiation also had higher odds of non-adherence, which is supported by studies showing that non-adherence rates increase over time (Lee et al., 2014; Wu et al., 2012). These results help to identify women who are at higher risk of unintentional non-adherence, and who may need further support in taking their medication, such as women in the workforce or women from minority ethnic groups. However, more research on these relationships is necessary before any specific recommendations can be made for improving adherence in these subgroups, especially with regards to the results around ethnicity. Results indicate unique correlates of intentional and unintentional non-adherence in this population, suggesting interventions tailored to the type of non-adherence may be necessary.

Women in their first six months since prescription showed more favourable beliefs and perceptions towards tamoxifen than those later in the treatment pathway. They have higher intentions to take tamoxifen, lower distress scores, lower scores on tamoxifen consequences and attributed fewer side-effects to tamoxifen. These results suggest that it may be beneficial to intervene early before women's intention to take tamoxifen decreases and to help them successfully manage their side effects early on. Interestingly, many of the illness perceptions were not significantly different which suggests beliefs may not change over the course of treatment, which is contrary to the self-regulation proposed by the CSM. However, longitudinal research is needed to confirm this.

This study included a large nationwide sample and is, to the best of our knowledge, the first study to investigate correlates of tamoxifen non-adherence from the CSM and TPB.

However, there were several limitations to the study. Adherence was measured by self-report, which may over-estimate adherence rates due to recall bias or socially-desirable answering. However, the MARS has been shown to correlate with more objective measures (O'Carroll et al., 2013), and non-adherence rates found in this study were comparable to studies using prescription refill rates (Partridge et al., 2003; Seneviratne et al., 2015). Taking less than 80% of prescribed doses is associated with decreased odds of survival in breast cancer patients (Hershman et al., 2011). Unfortunately we could not operationalise non-adherence in this way so it is unclear if the levels of non-adherence in this study are related to survival. Due to the cross-sectional design, it was also not possible to identify factors related to non-persistence. Future research should assess if the CSM and the TPB provide good explanation for non-persistence. We only tested illness and emotional representations within the CSM and missed other key elements of the model such as assessment of coping behaviours and appraisal. Although medication adherence could be seen as a coping behaviour used to control the health threat, we did not measure the appraisal of non-adherence as a coping strategy. The study was cross-sectional and it therefore limits assumptions about causality. Future research should test these models in longitudinal studies. Finally, there may be some selection bias, as the response rate was 61% and patients who did not take part may be more likely to be non-adherent.

In spite of these limitations, the study makes an important contribution to the literature by showing that the CSM and TPB provide a useful framework for understanding intentional non-adherence to tamoxifen. It highlights the utility of these theories and demonstrates the importance of considering both theories concurrently when designing interventions. Results also highlight the extent of non-adherence in this population and suggest that unintentional and intentional non-adherence may be distinct behaviours with unique correlates. In particular, the study highlights the high proportion of unintentional non-adherence. As this behaviour was not explained well by the psychological models, there is a need to further understand this behaviour and to develop ways to improve unintentional non-adherence. Future research should confirm these findings in longitudinal studies and use the CSM and the TPB as a framework for designing interventions to improve adherence to tamoxifen.

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6.3. Summary

The results from this chapter support the findings from the systematic review and qualitative study by showing that side effects and medication beliefs were both correlated with adherence, and were associated with intentional non-adherence in a logistic regression. However the relationship between side effect intensity and non-adherence was no longer significant when the CSM/TPB variables were added into the model. This supports the findings in the qualitative study which suggest that it may be more important to consider how women weigh their side effects up against their beliefs, rather than focussing solely on the presence or absence of side effects. It is therefore important for the intervention to target medication and illness beliefs as well as supporting women with their side effects. As side effects have been shown to be a key contributor to non-adherence, there was a need to investigate them further to explore the best ways to support women taking tamoxifen. The following chapter presents an analysis of the extent to which different side effects are experienced in this population. This provides important information on how to support women with tamoxifen side effects, which should help prevent women from becoming non-adherent.

The qualitative study showed that fear of recurrence is a motivating factor for women to take tamoxifen. This was supported in this analysis, with women who reported stronger beliefs in the risk of recurrence having lower odds of non-adherence. This study also builds upon the relationship found in the systematic review between social support and non-persistence, by showing that social support is also related to non-adherence. The systematic review found a relationship between self-efficacy for medication taking and non-adherence, which was supported here by the effect of PBC on adherence. Whilst slightly different concepts, these results suggest that an important determinant to HT adherence is the amount of control the patient feels they have over the medication taking behaviour. This finding has been replicated across other long term conditions (Brus, van de Laar, Taal, Rasker & Wigman, 1999; Holmes et al., 2014; Schoenthaler, Ogedegbe, Allagrante, 2006). Several demographic factors were associated with unintentional non-adherence, including not being white, being younger and being employed. Whilst these factors cannot be modified, they provide important information on who may be at risk of non-adherence. They also provide important information on how interventions may need to be tailored to support people most at risk of non-adherence.

The results from this chapter also present useful information for intervention development. The main conclusion is that key elements from the CSM and TPB provide a valuable framework for understanding tamoxifen non-adherence. The combined model, including

variables from the CSM and the TPB, explained more variance than either model alone. This suggests that interventions should draw on variables from both these theories, and target beliefs about illness and medication alongside perceptions of the actual medication taking behaviour. The results also confirm that perceptions around breast cancer are still relevant in Breast Cancer Survivors (BCS), which provides support for the CSM. The CSM and the TPB are very common and widely used in health psychology research. The results from this study suggest that the models are complemented by each other, and that combining elements from both models provides superior explanation of behaviour. Combining the models into one more parsimonious model may allow for greater prediction and understanding of non-adherence. When the models were combined, variables which were previously significant in the individual models did not remain significant. This suggests there may shared variance between the variables and that there may be some overlap across the models, thus supporting the need to create a more parsiminous model.

As well as confirming the hypothesis that the CSM and TPB are useful frameworks for intervention development, results from this study also highlight potentially modifiable factors which could be targeted in the intervention. The high percentage of unintentional non-adherence is also of great interest for intervention development, highlighting the need to focus on forgetting and establishing a good medication taking regimen. Women who had been taking tamoxifen for longer had higher odds of non-adherence, which suggests that there is a need to try and intervene early on in the treatment pathway to try and prevent women from becoming non-adherent later. This is supported by the finding that women in their first six months of tamoxifen had higher intentions to take tamoxifen and more favourable attitudes towards tamoxifen. They also experienced fewer consequences and attributed fewer symptoms to tamoxifen. This suggests that over time, women adjust their illness and treatment beliefs, which is consistent with the self-regulatory component of the CSM, although this needs to be confirmed in the longitudinal analysis. Clinically, this suggests that women are likely to feel more negatively about their treatment over time, increasing the likelihood of non-adherence. This supports the need to intervene early on in treatment before people's perceptions become more negative.

A limitation with this study was the fact that it is cross-sectional and therefore cause and effect cannot be inferred. To overcome this, a longitudinal study was conducted which is presented in Chapter 8. This analysis allows for examination of whether the associations found in the cross-sectional analysis are maintained over time. This analysis focussed on women in their first year of treatment, as studies show that the majority of women who discontinue HT do so within the first year (Fink et al., 2004; Huiart et al., 2012; Owusu et al., 2008) and that non-adherence rates increase significantly over time (Partridge et al.,

2003; Wu et al., 2012). Furthermore, the cross-sectional analysis showed that women in their first six months of treatment had significantly different perceptions than those later on in treatment. As this was not a longitudinal analysis, it is not possible to conclude if perceptions actually changed over time. A longitudinal design provides better testing of the self-regulatory component of the CSM. It was particularly pertinent to explore these changes over time in women near the beginning of treatment, as it is likely they will show more changes over time as they adjust to their treatment and assimilate new information and experiences. Understanding how their beliefs change will provide helpful information for how to support these patients.

7. Factors related to the experience of menopausal symptoms in women prescribed tamoxifen

7.1. Chapter Overview

The systematic review, qualitative study and cross-sectional study all highlighted side effects as a potential barrier to adherence. In order to gain greater understanding of the symptom burden women were experiencing, an additional analysis of the cross-sectional sample was conducted. This analysis is presented in the current chapter. The aims were to examine how prevalent different side effects were, how severe they were and whether they persisted throughout treatment. The study also explored factors associated with experiencing these symptoms and whether they were attributed to tamoxifen. The results from this study will be used to inform intervention development and to provide a context for interpreting results from the other studies.

7.2. Published paper

This chapter is published in the following article:

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Authors: Zoe Moon, Myra S Hunter, Rona Moss-Morris, Sophie Carlisle, Lyndsay D Hughes

Health Psychology Section, Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

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Corresponding author:
Lyndsay D Hughes
Health Psychology Section,
Institute of Psychiatry, Psychology & Neuroscience,
5th Floor Bermondsey Wing, Guy's Hospital,
London SE1 9RT, UK
Email lyndsay.hughes@kcl.ac.uk

Factors related to the experience of menopausal symptoms in women prescribed tamoxifen

Zoe Moon, Myra S. Hunter, Rona Moss-Morris and Lyndsay Dawn Hughes

ABSTRACT

Introduction: Menopausal symptoms are frequent and severe in breast cancer survivors taking tamoxifen; however, treatment options are limited for these patients as hormonal replacement therapy is contraindicated. This study aimed to explore the experience and attribution of menopausal symptoms and identify factors related to the experience of menopausal symptoms in women taking tamoxifen.

Methods: Women who had been prescribed tamoxifen for a diagnosis of primary breast cancer were recruited from oncology clinics across England and from online advertisements. Seven hundred and forty women completed questionnaires assessing illness perceptions, social support, mood and symptom duration/severity.

Results: Eighty-four percent of women had experienced hot flushes and 80% experienced night sweats; of these, 60% experienced severe symptoms. Symptoms persisted throughout 5 years of treatment and were mainly attributed to tamoxifen. Logistic regressions showed that depressive symptoms, previous chemotherapy and being employed were associated with increased odds of hot flush or night sweat prevalence. Symptom severity was associated with depression, being employed and attributing symptoms to tamoxifen.

Discussion: These findings have clinical implications in terms of targeting women who are more at risk and offering non-hormonal treatment options, such as cognitive behavioural therapy, to help women to develop self-management strategies for coping with menopausal symptoms

Introduction

Hot flushes and night sweats (HFNS), the main symptom of the menopause, typically involve a sudden sensation of heat and warmth, accompanied by reddening of the skin and sweating. They are thought to result from disturbances of the temperature regulating mechanism in the hypothalamus, triggered by reduced oestrogen levels [1]. Whilst HFNS can vary significantly between individuals, women with breast cancer are five times more likely than age matched controls to experience these symptoms and are also more likely to experience longer, more frequent and more severe HFNS [2–4]. Women who take tamoxifen are twice as likely to experience HFNS [2] and more likely to report severe to intolerable HFNS [5] than other breast cancer survivors.

Tamoxifen, or a similar class of drugs (aromatase inhibitors), are prescribed to up to three quarters of breast cancer survivors in order to reduce the risk of recurrence [6]. They are

prescribed to women with oestrogen receptor positive breast cancer and work by blocking the effects of oestrogen on cancer cells. Tamoxifen is prescribed mainly to pre-menopausal women, whereas aromatase inhibitors are prescribed only in post-menopausal women. Recent evidence suggests that survival benefits are enhanced if tamoxifen is taken for an additional 5 years [7,8]. This increase in treatment duration, accompanied by a rise in breast cancer survival rates, means that increasing numbers of women may be suffering from HFNS as a consequence of tamoxifen. Studies have indicated that HFNS prevalence in breast cancer survivors may be as high as 80% [9–11]. Tamoxifen is associated with a range of other side effects including weight gain, insomnia, joint pain and vaginal dryness [12,13]. Whilst not life threatening, these symptoms can have a considerable impact on quality of life [11]. HFNS in breast cancer survivors are associated with anxiety, sleep problems, poor emotional functioning [10] and poor physical health [14]. Furthermore, these symptoms can undermine adherence to tamoxifen [15,16].

One of the key treatments for HFNS, hormone replacement therapy (HRT) [17], is contraindicated in breast cancer survivors due to a potential increased risk of cancer recurrence, which severely limits treatment options for HFNS in these patients. There are some non-hormonal options, such as venlafaxine or gabapentin [18], but many breast cancer survivors are keen to avoid additional medications which likely have side effects [10]. Several recent papers have called attention to the lack of research into HFNS in breast cancer survivors [1,19] and highlighted a need to understand the experiences of these women, with a view to identifying safe and effective treatments [10,19,20].

Factors associated with HFNS in the general population include lower levels of education [21,22], African American race [23,24], younger age [25] and being without a partner [26,27]. The cognitive model of HFNS explains how the perception, attribution and appraisal of menopausal symptoms are influenced by cognitive factors, beliefs and mood [28]. For example, stress or negative affect can reduce the threshold for detection of physical sensations, and increase the likelihood that women will attend to, and therefore report, HFNS [28,29]. Anxiety has been shown to precede hot flushes [30]; however, studies suggest that there is a complex bi-directional relationship between HFNS and depression whereby HFNS can cause depressed mood, but may also be a result of depression [1,28,31].

Moreover, anxiety and depression are associated with negative beliefs, which in turn affect cognitive appraisal of symptoms [28]. For example, negative thoughts such as embarrassment, disgust and worry are linked to more problematic hot flushes [32]. The common sense model of illness representations posits that how patients represent symptoms and where they attribute them will likely guide how they cope with the symptom [33]. This may influence emotional reactions, illness outcomes and health behaviours such as treatment

adherence or help seeking [34–37]. The cognitive model of HFNS has informed the development of cognitive behavioural therapy (CBT) for HFNS, which has been shown to reduce the impact of HFNS [38,39].

Whilst the cognitive model of HFNS is well accepted in the general population [1,40], the experience of menopausal symptoms in women taking tamoxifen remains under-researched. This is important considering the increasing rates of breast cancer, partnered with greater survivorship and increased duration of tamoxifen treatment. This paper aimed to explore the experience and attribution of menopausal symptoms in women prescribed tamoxifen and, using the cognitive model and other sociodemographic predictors, identify factors related to the experience of HFNS.

Methods

The study was approved by the Northampton National Research Ethics Committee (Ref.: 14/EM/1207), with site specific approvals for each site.

Participants and procedure

Participants were recruited through oncology clinics in 27 NHS Trusts across England and through advertisements on Facebook groups, Twitter and charity websites between April 2015 and October 2015. To be eligible for the study, patients had to be female, over 18, have a diagnosis of primary breast cancer and currently being prescribed tamoxifen. Women were screened in clinic and those who were eligible were invited to participate in the study either in the clinic or with a postal invitation. Women who replied to the online advert were screened by the researcher. Informed consent was taken from all participants. The questionnaire took approximately 15–20 min to complete; participants could complete it in clinic or online, or take it away and return it to the researcher using a stamped addressed envelope. This formed part of a larger study investigating adherence to tamoxifen. Only measures relevant to this study are reported here.

Measures

Experience of menopausal symptoms

Participants were asked to indicate whether they had experienced symptoms using the identity scale from the Revised Illness Perceptions Questionnaire (IPQ-R [41]). This included the core symptoms from the IPQ-R as well as additional symptoms such as HFNS. Participants indicated whether they attributed symptoms to their breast cancer, their tamoxifen treatment or to previous cancer treatment. The additional concerns subscale from the FACT-ES [42] was used to measure the experience and severity of side effects. The FACT-ES is a quality of life scale for breast cancer patients taking endocrine therapy, with

good internal consistency and test–retest reliability [42]. Participants rated symptom severity on five-point scales, from "not at all" to "very much".

Potential predictors

Women were asked to provide sociodemographic data including their date of birth, age they left full-time education, relationship status, employment status, menopausal status (at diagnosis), date first prescribed tamoxifen and previous chemotherapy. Menopausal status was defined as pre-menopausal, menopausal or post-menopausal.

Mood

The Hospital Anxiety and Depression Scale (HADS [43]) was used to measure depression and anxiety. Each item is scored on a scale of 0–3, with higher scores reflecting higher levels of depression and anxiety. The scale has good internal consistency in patients with breast cancer [44,45].

Social support

The Multidimensional Scale of Perceived Social Support [46] was used to measure perceived social support. The scale has demonstrated good internal and test–retest reliability [46] and has been used successfully to measure social support in patients with breast cancer [47,48].

Statistical analysis

Statistical analyses were performed using SPSS v21 (SPSS Inc., Chicago, IL). For analysis of symptom prevalence, women were coded as experiencing a symptom if they had selected answers on the FACT-ES from a little bit to very much. For analysis of symptom severity, women who scored either of the top two answers (quite a bit/very much) were coded as experiencing severe symptoms and were compared to women experiencing mild to moderate symptoms (a little bit/somewhat). The attribution of symptoms was analysed using responses on the IPQ-R. Univariate logistic regressions were calculated to assess the relationships between predictor variables and HFNS prevalence. Predictor variables were chosen based on the cognitive model and previous literature identifying sociodemographic variables which may be related to HFNS. Variables tested in univariate analysis were age, ethnicity, age left full time education, relationship status, employment status, menopausal status (at diagnosis), chemotherapy, months since first prescribed tamoxifen, anxiety, depression, social support and whether symptoms were attributed to tamoxifen. Months since first tamoxifen prescription, social support and depression were skewed and log transformations were performed. Variables which showed a significant relationship in univariate analysis were entered into a final multivariate model. Categorical variables such as ethnicity were

converted into dichotomous dummy coded variables. The same analysis was then conducted to predict experience of severe HFNS in subgroup analyses of participants who had experienced these symptoms.

Results

Participant rate

One thousand two hundred and twenty-eight women were posted information about the study or approached in clinic. Seven hundred and forty-six women from 27 centres across England returned the questionnaire, giving a response rate of 61%. An additional six questionnaires were received from a site with no response rate information. Sixty-one women were recruited online. Once women who had reported discontinuing tamoxifen were removed (n=73), the sample consisted of 740 women.

Table 1. Demographics of study population

	N (%)
Age, mean (SD)	53 (10 Range 30-90
Ethnicity	
White British	681 (92%)
Mixed/multiple ethnic	7 (1%)
Asian/Asian British	30 (4%)
Black/Black British	12 (2%)
Other ethnic background	10 (1%)
Relationship status	
Single	79 (11%)
Married	431 (58%)
Widowed	34 (5%)
Separated/divorced	91 (12%)
Cohabiting	102 (14%)
Employment status	
Employed full time	281 (38%)
Employed part time	204 (28%)
Homemaker	52 (7%)
Unemployed	57 (8%)
Retired	114 (15%)
Other	30 (4%)
Age left full time education	
Under 18	366 (49%)
Over 18	376 (51%)
Menopausal status at diagnosis	
Pre-menopausal	405 (55%)
Peri-menopausal	83 (11%)
Post-menopausal	202 (27%)
Unsure / missing	50 (7%)
Months since prescribed tamoxifen, mean (SD)	19.5 (18.3) Range 0.2-121
Received chemotherapy	381 (52%)

Sample characteristics

The mean age was 53 (SD=10, range 30–90) (Table 1). Women were diagnosed with stage I to stage III breast cancer and were prescribed tamoxifen. The majority of participants were married/cohabiting (72%) and were employed (66%). Forty-nine percent left full time education under the age of 18. Over half of women were pre-menopausal at diagnosis (55%) and had been treated with chemotherapy (52%). Women had been taking tamoxifen for on average 20 months (SD=18, range 0.2 months to 10 years).

Experience, attribution and duration of menopausal symptoms

A high percentage of participants had experienced hot flushes (84%) and/or night sweats (80%) and around 60% of these had experienced severe HFNS (Table 2). Patients also self-reported experiencing the following symptoms from the FACT-ES; fatigue (53%), weight gain (66%), mood swings (67%), loss of libido (68%), vaginal dryness/discharge/itchiness (72%) and joint pain (72%). All symptoms were attributed to tamoxifen more often than to breast cancer or previous cancer treatment. The symptoms most commonly attributed to tamoxifen on the IPQ-R were hot flushes (66%), night sweats (54%), weight loss/gain (40%), joint pain (37%), fatigue (35%), sleep difficulties (34%), vaginal dryness/discharge/itchiness (34%) and change in sex drive (27%). Figure 1 shows that the prevalence of HFNS is high across participants at different time points of treatment, including those in their fifth year. In separate analyses of those who had experienced symptoms (n=623 for HF/n=587 for NS), the proportion of women experiencing severe symptoms remains relatively high across the 5 years, but begins to decrease slightly at 4 years of treatment (Figure 2).

Factors related to prevalence of HFNS

In the univariate analysis, younger age (OR=0.95, 95% CI=0.93–0.97), being employed (OR=3.74, 95% CI=2.45–5.72), being premenopausal at diagnosis (OR=1.95, 95% CI=1.29–2.94), receiving chemotherapy (OR=3.13, 95% CI=2.04–4.80) and having higher levels of anxiety (OR=1.09, 95% CI=1.04–1.15) and depression (OR=1.90, 95% CI=1.24–2.90) were significantly related to hot flush experience (Table 3). These variables were entered into a logistic regression model, which explained 15% of the total variance (Nagelkerke R^2). Women who were employed (OR=2.65, 95% CI=1.44–4.90), who scored higher on the HADS depression scale (OR=2.22, 95%CI=1.33–3.70) and who had chemotherapy (OR=1.93,95% CI=1.14–3.26) were around twice as likely to experience hot flushes (Table 4).

Table 2. Experience and attribution of symptoms

	FACT-ES		IPQ-R		
	% experie-nced in past seven days	% with moderate to severe symptoms	% attributed to breast cancer	% attributed to previous breast cancer treatment	% attributed to tamoxifen treatment
Hot flushes	84	64	9	8	66
Night sweats	80	60	7	7	54
Change in sex drive†	40	-	1%	8	27
Loss of sex drive	68	46	-	-	-
Pain or discomfort with intercourse	41	40	-	-	-
Vaginal discharge / dryness/ itchiness	72	39	5	5	34
Weight gain	66	46			
Weight loss / gain†	47	-	10	10	40
Feeling down†	37	-	18	8	20
Mood swings	67	30		-	-
Fatigue†	53	-	19	13	35
Sleep difficulties†	44	-	13	9	34
Joint pain	72	55	6	14	37
Headaches	53	21	3	8	15
Loss of concentration†	38	-	12	9	24

Not all women who reported a symptom will have reported how they attributed it, and women could select multiple sources of attribution. % with moderate to severe symptoms in separate analysis of only those who experienced symptom. †these symptoms are not included in the FACT-ES and prevalence is derived from the IPQ-R.

Figure 1. Percentage of women taking tamoxifen who reported hot flushes or night sweats

In the univariate analysis (Table 3), experience of night sweats was related to younger age (OR=0.97, 95% CI=0.95–0.98), being employed (OR=2.41, 95% CI=1.63–3.56), being premenopausal (OR=1.46, 95% CI=1.00–2.11), being without a partner (OR=0.63,95% CI=0.43–0.92), receiving chemotherapy (OR=1.91, 95% CI=1.32–2.74) and higher levels of anxiety (OR=1.11, 95% CI=1.06–1.16) and depression (OR=2.42, 95% CI=1.51–3.32). These variables were entered into a logistic regression model which accounted for 12% of the total variance; women with more depressive symptoms (OR=2.41, 95% CI=1.34–4.33) and who were employed (OR=2.18, 95% CI=1.24–3.82) were more likely to experience night sweats (Table 4).

Factors related to severity of HFNS

In the univariate analysis of those who experienced hot flushes (n=623), hot flush severity was associated with being employed (OR=1.62, 95% CI=1.07–2.43), premenopausal (OR=1.52, 95% CI=1.07–2.14), having chemotherapy (OR=1.56, 95% CI=1.12–2.17), higher levels of anxiety (OR=1.07, 95% CI=1.03–1.11) and depression (OR=2.04, 95% CI=1.45–2.87) and attributing hot flushes to tamoxifen (OR=2.58, 95% CI=1.77–3.77) (Table 5). Variables were entered into a final model which explained 18% of the variance in hot flush severity (Table 4). Women who attributed their hot flushes to tamoxifen were almost four times more likely to experience more severe hot flushes (OR=3.78, 95% CI=2.43–5.77) and women who had more depressive symptoms (OR=1.99, 95% CI=1.22–3.24) or were employed (OR=1.68, 95% CI=1.03–2.73) were almost twice as likely to experience severe hot flushes.

In the univariate analysis of participants who experienced night sweats (n=587), anxiety (OR=1.06, 95% CI=1.02–1.11), depression (OR=2.03, 95% CI=1.46–2.83) and attribution of night sweats to tamoxifen (OR=2.63, 95% CI=1.84–3.74) were related to night sweat severity. All variables except anxiety remained significant in the multivariate analysis, accounting for 11% of the total variance (Table 4). Attributing night sweats to tamoxifen (OR=2.80, 95% CI=1.94–4.01) and depression (OR=1.10, 95% CI=1.03–1.17) were both linked to increased odds of severe night sweats.

Discussion

This paper examined the experience of menopausal symptoms in breast cancer survivors taking tamoxifen and explored factors contributing to the experience of HFNS. Results showed that 84% of women had experienced hot flushes and 80% had experienced night sweats. This is consistent with previous research in the community indicating a prevalence of around 80% [9–11], but is much higher than the prevalence of 29–45% found in several large RCTs comparing tamoxifen with aromatase inhibitors [49]. This may be because some

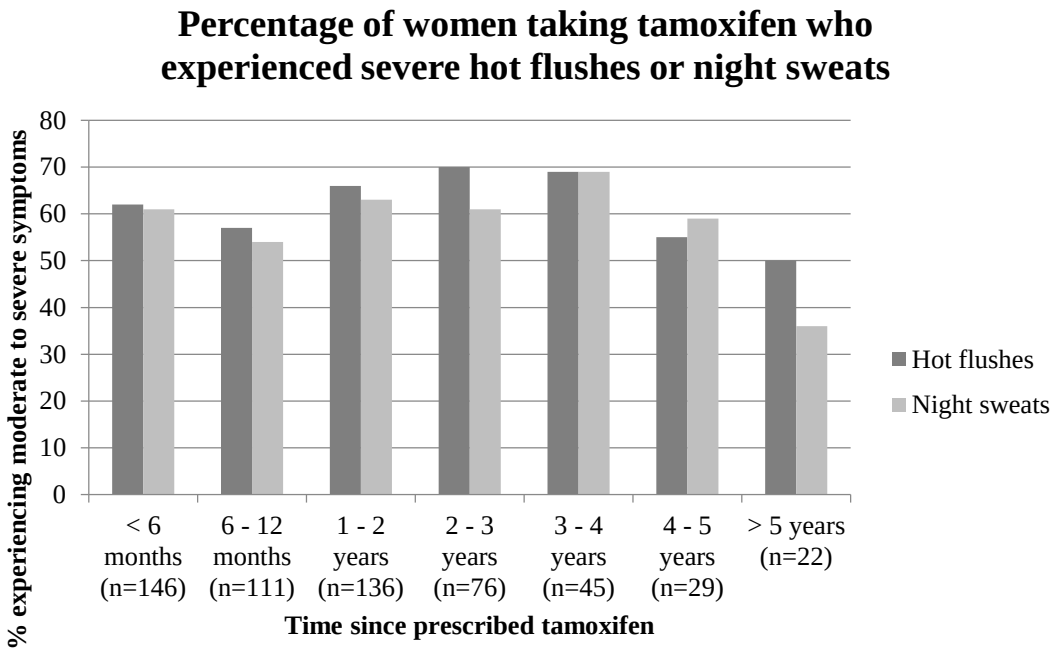

Figure 2. Percentage of women taking tamoxifen who reported severe hot flushes or night sweats.

Table 3

Univariate regressions predicting prevalence of HFNS

	Hot flushes		Night sweats	
	OR	95% CI	OR	95% CI
Age	0.95**	0.93 – 0.97	0.97**	0.95 – 0.98
Ethnicity Other vs. white British	1.18	0.68 - 2.06	1.16	0.70 –1.92
Age left full time education < 18 vs 18 +	1.05	0.71 – 1.55	1.00	0.70 – 1.42
Employment status Employed vs not employed	3.74**	2.45 – 5.72	2.41**	1.63 – 3.56
Marital status No partner vs. partner	0.80	0.52 – 1.23	0.63*	0.43 – 0.92
Menopausal status Pre vs. post-menopausal	1.95*	1.29 – 2.94	1.46*	1.00 – 2.11
Chemotherapy	3.13**	2.04 – 4.80	1.91**	1.32 – 2.74
Months since prescribed	1.10	0.99 – 2.23	1.03	0.94 – 1.13
HADS anxiety	1.09*	1.04 – 1.15	1.11**	1.06 – 1.16
HADS depression	1.90*	1.24– 2.90	2.42**	1.51 – 3.32
Social support	1.35	0.97 – 1.89	1.15	0.85 – 1.54

Note. ** p < .001 , * p < 0.05

Table 4

Multivariate regressions predicting prevalence/severity of HFNS

	Hot flushes prevalence		Night sweat prevalence		Hot flush severity		Night sweat severity	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Employment status (employed vs not employed)	2.65*	1.44 – 4.90	2.18*	1.24 – 3.82	1.68*	1.03 – 2.73		
Chemotherapy	1.93*	1.14 – 3.26						
HADS depression	2.22*	1.33 – 3.70	2.41*	1.34 – 4.33	1.99*	1.22 – 3.24	1.10**	1.03 – 1.17
Attributing HF/NS to tamoxifen					3.78**	2.43 – 5.77	2.80**	1.94 – 4.01

Note. ** p < .001 , * p < 0.05

Table 5

Univariate regressions predicting severity of hot flushes (n = 623) and night sweats (n=587)

	Hot flushes		Night sweats	
	OR	95% CI	OR	95% CI
Age	0.98	0.97 – 1.00	0.98	0.97 – 1.00
Ethnicity Other vs. white British	1.24	0.77 - 1.99	1.39	0.86 – 2.24
Age left full time education < 18 vs 18 +	1.07	0.77 – 1.48	1.28	0.92 – 1.78
Employment status Employed vs not employed	1.62**	1.07 – 2.43	1.23	0.81 – 1.87
Marital status No partner vs. partner	0.87	0.60 – 1.25	0.86	0.59 – 1.25
Menopausal status Pre vs. post-menopausal	1.52*	1.07 – 2.14	1.31	0.92 – 1.85
Chemotherapy	1.56*	1.12 – 2.17	1.06	0.76 – 1.47
Months since prescribed	1.02	0.94 – 1.12	1.00	0.92 – 1.09
HADS anxiety	1.07*	1.03 – 1.11	1.06**	1.02 – 1.11
HADS depression	2.04**	1.45– 2.87	2.03**	1.46 – 2.83
Social support	1.56	0.93 – 2.62	1.14	0.69 – 1.91
Symptom attributed to tamoxifen	2.58**	1.77 – 3.77	2.63**	1.84 – 3.74

Note. ** p < .001 , * p < 0.05

women who experienced negative side effects discontinued treatment and were removed from the RCTs.

However, previously, less was known regarding the severity of HFNS in women taking tamoxifen [50]. This paper adds new information, by showing that around 60% of women experiencing HFNS reported severe symptoms. The extent and severity of these symptoms

reinforces the need to identify who is more at risk and to find ways to help patients manage these symptoms [1,19,20]. Participants also reported high levels of joint pain, vaginal discharge/dryness/itchiness, loss of libido, mood swings and weight gain. The prevalence of fatigue and sleep problems was slightly lower than previously reported in patients taking tamoxifen [13,51], but loss of libido, vaginal symptoms and mood swings were higher than previous reports have indicated [13,52,53]. Again, all symptoms were reported at a greater frequency than found in a review of RCTs [49].

Previous studies have suggested that HFNS are less problematic after one year of tamoxifen treatment [54,55] and patients are often advised that their symptoms will reduce after a few months. However, this study shows that the prevalence of HFNS remains stable (around 80%) regardless of whether the patient is in her first or fifth year of treatment. The severity of symptoms also remains high up until the fourth year of treatment. This highlights the need to identify effective strategies to help women to manage their HFNS across the duration of treatment. CBT has been shown to reduce HFNS frequency and problem rating in breast cancer survivors and can teach women long-term self-management strategies [38,39,56].

Up to two-thirds of participants attributed HFNS to tamoxifen. Participants also associated other symptoms to tamoxifen, including fatigue, sleep difficulties, joint pain, vaginal discharge/dryness/itchiness and weight loss/gain. These symptoms are established side effects of tamoxifen [13]. Women who attributed HFNS to tamoxifen were three to four times more likely to experience severe symptoms than those who did not attribute their symptoms to tamoxifen. More research is needed to confirm the direction of this effect and to establish the consequences of attributing symptoms to tamoxifen treatment. Previous studies have suggested that symptom attribution is likely to affect coping behaviours [33], but this was not tested in the current study.

After controlling for demographic factors and mood, women who had chemotherapy were twice as likely to report hot flushes than women who had not had chemotherapy. This conflicts with previous studies in breast cancer patients, showing no association between HFNS and chemotherapy [11,57]. However, previous studies included mainly postmenopausal women, and the association between chemotherapy and HFNS may be stronger in premenopausal women [58]. Chemotherapy can induce an early menopause in some patients, increasing the incidence of HFNS [59], which could explain the increased HFNS in premenopausal women who have received chemotherapy.

Women who were employed were twice as likely to experience HFNS and more likely to experience severe hot flushes. This has important implications for supporting women in the workplace. Studies have shown that menopausal symptoms cause difficulty at work and may

impact negatively on work performance [1,60,61]. Working women have discussed fears around embarrassment and others' reactions [62], which is likely to exacerbate the severity of hot flushes. CBT may be helpful to moderate negative thoughts around menopausal symptoms in the workplace and to reduce anxiety around stigma.

Higher scores on the depression scale were associated with twofold increased odds of HFNS incidence and increased odds of severe HFNS. This supports the cognitive model of HFNS [28], which proposes that depressed mood can affect how patients perceive and appraise their symptoms. However, it is likely that there is a bi-directional relationship between HFNS and depression, and it is unclear in this study if the depressed mood is a result of the HFNS or if it is increasing the likelihood that women will report symptoms. Anxiety was associated with increased odds of HFNS in the univariate analysis, but was not significant after controlling for other variables. This contrasts with previous studies showing a clear relationship between anxiety and hot flushes [30]. However, the lack of relationship between anxiety and HFNS has been shown previously in breast cancer patients [63].

Age was significantly related to HFNS prevalence in the univariate analysis, but was not significant in the multivariate analysis. This is likely due to shared variance between age and menopausal status at diagnosis. Younger age has been found to be associated with increased risk of hot flushes in breast cancer survivors [5]; however, this effect has not been consistently shown [11,13]. Previous studies have shown that ethnicity is related to hot flush frequency [64]. African-American women tend to report more hot flushes than Caucasian women and Japanese women have been shown to report fewer symptoms [24,65,66]. However, these effects are not always shown [67] and the current study found no effect of ethnicity on HFNS prevalence or severity. This may be due to the lack of ethnic diversity in the study; only 8% of women self-identified as not White British.

Overall, the results suggest that a high proportion of women experience symptoms such as HFNS as well as fatigue, joint pain and vaginal symptoms. These symptoms are often severe and women report experiencing them even in their fifth year of treatment. As HRT is contraindicated, only 21% of breast cancer survivors receive any treatment for these symptoms [11] and there is a need to identify non-hormonal treatments. The North American Menopause Society (NAMS) has reviewed evidence for non-hormonal treatments and has found some degree of efficacy for selective serotonin reuptake inhibitors in menopausal women [68], but results are not conclusive and breast cancer survivors have expressed a preference for nonmedical treatments [10]. CBT, which is based on the cognitive model of HFNS, is recommended by NAMS [69] and The National Institute for Health and Care Excellence [17]. CBT has been shown to improve HFNS problem rating and may provide patients with long lasting self-management strategies. There is a need to

identify patients who are taking tamoxifen and have received chemotherapy, as they may be more at risk of hot flushes. Furthermore, the results stress a need to support women who have returned to work following breast cancer.

The strengths of this study were the large sample size, use of validated measures and good response rate. This is one of the largest samples used to investigate the experience of HFNS in women taking tamoxifen. However, that we measured symptom severity and not bother is a limitation of this study. Measuring perceived bother from symptoms as opposed to the severity may provide a more thorough understanding of the impairment associated with these symptoms [66]. An additional limitation was the use of cross-sectional data which prohibits causal assumptions for some effects, such as the relationship between hot flushes and depression. All measurements were subjective; therefore, the hot flush frequency may be more of an assessment of how people perceive their symptoms rather than an objective physiological measure. Data were not collected on use of additional medications. Some women may be prescribed antidepressants to manage their HFNS, and this could have impacted on their mood. A final limitation with the study was the lack of a comparison group, such as breast cancer patients not receiving endocrine therapy, with whom to compare the results to.

Conclusion

Prevalence and severity of HFNS, as well as other symptoms such as vaginal dryness and joint pain, are high in breast cancer survivors taking tamoxifen. There is a need to identify non-hormonal treatment options such as CBT to help support patients with these symptoms, especially as they persist for longer than previously believed. Furthermore, this study shows that women who are in employment, received chemotherapy, attribute HFNS to tamoxifen and have high depression scores may require more targeted support to manage HFNS.

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7.3. Summary

The results from this paper provide interesting context for the symptom experience of Breast Cancer Survivors (BCS) taking tamoxifen. A very high proportion of participants experienced HFNS, and over half of these had experienced severe HFNS. As previous research has shown some relationship between side effects and adherence, this indicates the need to address these symptoms in the intervention. This finding supports the results of the qualitative study which showed that women reported a high symptom burden. The results from this analysis also highlight additional common side effects which will be targeted in the intervention: fatigue; weight gain; mood swings; loss of libido; vaginal dryness/discharge/itchiness and; joint pain. It is also of interest that many women attributed these symptoms to tamoxifen. This suggests that experience of these symptoms may be contributing to any negative emotions regarding tamoxifen. Whether attributing symptoms to tamoxifen has any negative impact on adherence will be assessed in the following chapter.

Another finding which is particularly relevant for intervention development is the finding that the prevalence of HFNS is high across all time points, including those in their fifth year of treatment. This contrasts with the previous consensus that side effects would likely abate over time, and suggests that there is a need to support women throughout their treatment trajectory. The previous chapters have shown that many women continue with treatment, despite experiencing side effects. This current chapter has shown that these side effects are very common and are often severe. There is a need to understand why some women are motivated to continue with treatment, even when experiencing these side effects. Fully understanding these psychological components will inform the best way to support these women.

8. Psychosocial predictors of non-adherence to tamoxifen in breast cancer survivors: A longitudinal analysis

8.1. Background

Previous research into psychosocial predictors of tamoxifen adherence has largely been cross-sectional and lacking a theoretical framework. Chapter 6 showed that the Common Sense Model (CSM) and the Theory of Planned Behaviour (TPB) are useful frameworks for understanding tamoxifen non-adherence, but as this research was cross-sectional, it is not possible to infer causality. From cross-sectional studies, it is unclear if a certain illness perception may be causing someone to become non-adherent, or if they hold that illness perception because they are non-adherent. Longitudinal studies allow researchers better examination of causal relationships between potential predictor variables and non-adherence. This provides important information for intervening to improve adherence rates. In order to design effective interventions, it is important to understand if a change in a variable may be associated with a change in adherence levels.

Furthermore, longitudinal designs allow for examination of changes over time. Following the assumptions of the CSM, there is reason to believe that both illness representations and coping methods will change over time as new knowledge and experiences are evaluated and incorporated. Longitudinal analysis allows for examination of these changes. Leventhal proposed that illness representations could be updated at any time, based on new information from family, friends, Healthcare Professionals (HCPs) or the media (Leventhal et al., 2016). These changes to illness representations will likely cause changes to coping methods. For example, if a patient is exposed to new information suggesting that cancer is caused primarily by poor diet, they may adjust their illness representations to account for this, and may therefore feel that adhering to their Hormone Therapy (HT) is no longer an appropriate response to the illness threat. Likewise, the appraisal of coping strategies can also cause changes to illness representations, where patients may re-evaluate their perception of the illness based on the success or failure of coping strategies. Despite these being key assumptions of the CSM, very few studies have tested these relationships longitudinally, especially with regards to their effects on medication adherence.

There is some evidence to suggest that both illness perceptions and medication beliefs change over the illness trajectory. For example, Bijsterbosch et al. (2009) examined illness perceptions in 241 patients with osteoporosis. Over a six year period, there were small but significant changes in illness perceptions. Patients felt they had less personal control over their illness, they had less strong emotional representations and their chronic timeline beliefs

increased. In oesophageal cancer survivors, treatment control, consequences and identity all decreased over time (Dempster et al., 2011). However, other studies have shown that illness representations remain stable over time (Foster et al., 2008; Massey et al., 2013; McCorry et al., 2013a; Rutter & Rutter, 2007). The inconsistency across studies suggests that the dynamic nature of the CSM may vary across conditions or populations, with more stable or asymptomatic illnesses seeing little change over time, but progressive illnesses seeing more variation in illness perceptions over time. Studies also differ in the time in which they recruited participants. It may be that illness perceptions show significant variation immediately after diagnosis as an individual adjusts to the illness and experiences a vast amount of change, but are stable later in treatment as their condition also becomes more stable. Mixed results are also found for the dynamic nature of medication beliefs, with some studies showing variation over time (Massey et al., 2015; Shiyanbola, Farris & Chrischilles, 2013) and others showing relatively stable beliefs (Gonzalez et al., 2007).

A small amount of research has examined longitudinal relationships between illness perceptions and treatment adherence. A recent meta-analysis found weak relationships between illness perceptions and self-management behaviours across a range of both acute and chronic illnesses (Aujla et al., 2016). However, as discussed in Chapter 2, the relationships between illness perceptions and self-management behaviours can vary considerably across illnesses and illness contexts and therefore it does not make theoretical sense to combine results across this many illnesses and behaviours. Schuz, Wolff, Warner, Ziegelmann and Wurm (2014) found that timeline and control beliefs predicted adherence six months later in older adults with multiple illnesses. Van der Have et al. (2016) studied 126 patients with Inflammatory Bowel Disease and found that stronger timeline perceptions and stronger emotional responses predicted non-adherence over the following twelve months. However, some studies found no significant relationships between illness perceptions and later adherence (French, Wade & Farmer, 2013; Massey et al., 2015).

With regards to medication beliefs, there is some evidence to suggest that baseline medication beliefs predict later adherence. Horne, Cooper, Gellaitry, Date and Fisher (2007) found that concerns and necessity beliefs were predictive of Highly Active Antiretroviral Therapy adherence in people with HIV 12 months later, after controlling for depression and key clinical variables. Zwikker et al. (2014a) reviewed the literature and concluded that the majority of studies found no significant effects for the relationship between medication beliefs and later non-adherence. However, the majority of these studies did not use the Necessity Concerns Framework (NCF) as a framework and did not use a validated tool to measure medication beliefs. Since Zwikker's review, several studies have supported the assumption that baseline medication beliefs are associated with later non-adherence

(Gonzalez et al., 2007; Kalichman et al., 2015; O'Carroll et al., 2011; Ruppar, Dobbels & De Geest, 2012). For example, increases in necessity and concern beliefs over three months were associated with increased and decreased odds of adherence respectively in patients with acute coronary syndrome (LaPointe et al., 2011). However, some recent studies have found no significant relationship between medication beliefs and adherence over time (French et al., 2013; Massey et al., 2015; Schuz et al., 2014; Trachtenberg et al., 2012). Therefore, further research is needed to establish the longitudinal relationship between medication beliefs and adherence.

However, the research is a little clearer in Breast Cancer Survivors (BCS) taking Hormone Therapy (HT). Fink et al. (2004) investigated the relationship between medication beliefs and persistence in breast cancer survivors prescribed tamoxifen. They followed up 516 women over the age of 65 for two years. By the second year, 16% had discontinued treatment, and this was predicted by having a neutral or negative decisional balance score at the previous time point (OR=3.3, 95% CI=1.8-5.9). Similar effects were found in the five year analysis, with 31% of the sample discontinuing tamoxifen (Lash et al., 2006). Patients who had a positive view of tamoxifen at baseline (HR for a ten-point higher score=0.93, 95% CI=0.83-1.0) and patients with an improving attitude towards tamoxifen (HR for a 10-point change = 0.93, 95% CI=0.87-1.00) were less likely to discontinue. Bender et al. (2014) found no effects of necessity or concerns on adherence measured using Medication Event Monitoring System (MEMS) over an 18 month period. However, the lack of effects may be due to the very high levels of adherence found (96% of days with correct intake). Hershman et al. (2016) followed 523 women over two years, and found that positive attitudes to HT at baseline were associated with decreased odds of non-persistence over a two year follow up, after controlling for income and age (OR=0.51, 95% CI=0.32-0.81).

The TPB assumes less of a dynamic nature between components. However, it could be presumed that Perceived Behavioural Control (PBC) may increase over time as people become more confident about taking their medication, and that attitudes and subjective norms may vary over time, depending on external influences such as information from the media, HCPs or friends. As with the CSM, the majority of research investigating the relationship between adherence and the TPB is cross-sectional (Schwarzer, 2014). One longitudinal study found that baseline intentions were predictive of immunosuppressant therapy adherence measured over three months with prescription refill rates (Chisholm et al., 2007). However, another found that intentions did not predict later adherence in patients with type 2 diabetes (Zomahoun et al., 2016). The current study is the first to test these constructs longitudinally in women with breast cancer.

8.1.1. Aims and hypotheses

There is evidence that the CSM and the TPB are useful frameworks for investigating tamoxifen non-adherence in cross-sectional analyses. However, little research has tested these models longitudinally. There is some evidence that beliefs about tamoxifen are related to later non-persistence (Fink et al., 2004; Lash et al., 2006) but these studies only measured persistence and not adherence and did not use the NCF as a framework. This study aimed to examine longitudinal associations between psychosocial predictor variables and tamoxifen non-adherence. Studies have shown that the majority of women who discontinue HT do it within the first year (Fink et al., 2004; Huiart et al., 2012; Owusu et al., 2008) and that non-adherence rates increase significantly over time (Partridge et al., 2003; Wu et al., 2012). Furthermore, it is likely that there will be changes in illness perceptions whilst patients are still relatively early on in treatment. Therefore, it is important to study relationships between beliefs and adherence in the first few years of treatment.

The aims of this study were:

a) To examine changes in adherence over time in a sample of women newly prescribed tamoxifen.
b) To identify if illness perceptions and treatment beliefs from the CSM change over time.
c) To test the CSM and TPB longitudinally to examine if the relationships found between the CSM and TPB constructs and adherence at baseline will extend to longitudinal analysis.

There is currently a lack of evidence examining how TPB constructs change over time. Therefore, some hypotheses are based on theoretical assumptions rather than previous empirical evidence. However, based on previous research, it was possible to make a series of hypotheses regarding adherence and the CSM:

a) Based on previous research, it is expected that non-adherence rates will increase significantly over time.
b) It is expected that breast cancer consequences will decrease over time, as time from initial treatment lengthens. Based on evidence in Chapter 7 showing a high symptom burden across treatment, it is expected that tamoxifen consequences and identity will remain stable. Likewise, it is expected that risk of recurrence and cure beliefs will remain stable, as evidence suggests that perceived risk of recurrence remains high many years after primary treatment.

c) As previously argued, we hypothesise that PBC may increase over time as participants get more confident in their abilities to take the medication.
d) Based on associations between medication beliefs and tamoxifen non-persistence, it is hypothesised that the necessity/concerns differential will remain a significant predictor of non-adherence in the longitudinal analysis.
e) It is hypothesised that the models will complement each other and that constructs from both models, such as medication beliefs and PBC will predict non-adherence.

8.2. Methods

8.2.1. Participants

Recruitment methods are described in Chapter 6 (Section 6.2). Participants from the cross-sectional study who were within their first year of treatment and who had not already discontinued tamoxifen were sent follow up questionnaires (*n*=345).

8.2.2. Procedure

Participants consented to being sent follow up questionnaires when they were recruited into the larger cross-sectional study. Full NHS REC and HRA approval was granted as part of the cross-sectional study (REF 14/EM/1207). Participants were sent questionnaires at 3, 6 and 12 months. The questionnaire was identical to the one used in the cross-sectional study as described in Chapter 6, but the questions relating to demographic and clinical variables were removed in the follow up questionnaires. The questionnaires were either emailed or posted depending on the participant's preference. If the questionnaire was not completed within two weeks, a reminder email or letter was sent. If the questionnaire was still not received after a further two weeks, phone calls were made to remind the participant. Participants were removed from the study and not sent further questionnaires if they reported discontinuing tamoxifen at the previous time point or if they expressed a desire to withdraw from the study.

8.2.3. Statistical analysis

The sample size for the study was determined using G*Power 3.1.9.2, on the basis of a medium effect size. This was determined through the small amount of previous research investigating the psychosocial correlates of tamoxifen non-adherence (Grunfeld et al., 2005; Arriola et al., 2014). Assuming a medium effect size, testing the two models of health behaviour, with a maximum of 19 tested predictors, the sample size needed to achieve 90% power at a 0.05 level of significance was 187 participants. Based on attrition rates in similar

studies in BCS, we expected 40% attrition over a twelve month period. Therefore, a baseline sample size of 320 participants was needed.

Participants were categorised as adherent or non-adherent following the same guidelines as in the cross-sectional analyses (Section 6.2). Non-adherence rates for total non-adherence, intentional non-adherence and unintentional non-adherence were calculated for each time point. Women who had discontinued tamoxifen were asked to provide a free text response to detail their reason for discontinuing. This was to determine whether women had made an intentional decision to discontinue treatment or if they were switched onto another medication or discontinued by their doctor due to contraindications. The percentage of women who intentionally discontinued during the study period was very low and therefore it was not possible to predict discontinuation. Instead, these women were classed as non-adherent in the latent growth models. Therefore, the term "non-adherent" is used to capture all participants who were not taking their medication, both permanently and intermittently. One-way repeated measures ANOVAs were used to analyse changes in psychosocial variables over time, using post-hoc tests with Bonferroni correction. Where the assumption of sphericity was violated, the Hunyh-Feldt or Greenhouse-Geisser corrections were used.

Latent growth models (LGMs) were carried out to model the change in non-adherence rates over time and to identify factors associated with this change. In LGMs, initial status and growth over time are both modelled as latent variables. With this analysis, it is possible to identify:

1. The initial starting point of non-adherence (the intercept)
2. Variance within the initial stating point
3. How non-adherence changes over time (the slope)
4. Whether there are individual differences in the rate of change
5. Whether there is a relationship between the intercept and slope
6. Predictors of both the intercept and the slope

This analysis was carried out in Mplus v7. The four non-adherence time points were set to load onto the slope at 0,3,6 and 12 to represent the timings between measurements (i.e. 0,3,6,12 months). All loadings onto the intercept factor were automatically fixed to 1. The mean of the intercept was constrained to 0, but the mean of the slope, the variances of the slope and the intercept and the correlation between the slope and the intercept were estimated. The analysis was conducted in two steps. The first step was to establish the model of change for an unconditional model just including the non-adherence values. A linear model of change was tested and then compared to a model adding a quadratic growth factor,

to assess the function of growth over time. Model fit was compared using the BIC and loglikelihood values, with lower values indicating superior model fit.

The second step was to add potential covariates to the model. Covariates were able to predict both the intercept and the slope. All covariates were measured at baseline. Bivariate associations were carried out, and any variable showing a significant effect at $p \leq 0.10$ were included in the final model. This slightly less stringent alpha value was set to improve chances of identifying all relevant variables, as studies suggest that alpha values of <0.05 can miss important variables (Bursac, Gauss, Williams, & Hosmer, 2008). The data meets the minimum level of three observations required to test a hypothesis of linearity (Preacher, 2010) and has a sample well above 100, which is preferred for LGMs (Curran, Obeidat & Losardo, 2010). The LGM analysis steps were repeated to analyse intentional and unintentional non-adherence separately.

Once the final LGMs had been constructed to test the CSM and the TPB, the predictive probabilities generated from these two models were exported from Mplus into Stata v14.2. A ROC analysis was run on the predictive probabilities. This analysis tests the accuracy of the two models to discriminate between adherent and non-adherent participants. Scores range from 1, which indicates perfect discrimination, to 0.5, which indicates a model with no discriminative ability better than chance.

The variable *intentions* from the TPB was removed from the LGM analysis as it was strongly positively skewed and showed high kurtosis.

8.3. Results

8.3.1. Response rate

The flow of participants through the study is summarised in Figure 8.1. 345 participants were eligible for the longitudinal study and were sent the 3 month follow up questionnaire. Of these, 315 were returned, giving a 91% response rate. Of the 30 questionnaires which were not returned at 3 months, 29 (8%) were lost to follow up and one patient was deceased. At the 3 month point, 11 (3%) participants reported discontinuing tamoxifen and one requested to withdraw from the study. Therefore, only 332 6 month questionnaires were sent. 286 questionnaires were returned (response rate 86% of those sent out, 83% of total sample). Reasons for not returning the questionnaire at 6 months were withdrawing from study (*n*=1), discontinued tamoxifen (*n*=7), patient deceased (*n*=1) and loss to follow up (*n*=37). Again, a number of participants reported discontinuing tamoxifen (*n*=22, 7%) or withdrew from the study (*n*=5) and therefore only 306 12 month questionnaires were sent. Of these, 258 were returned and 48 were not returned. Reasons for not returning

questionnaires were withdrawing from the study (*n*=1), patient deceased (*n*=1), discontinued tamoxifen (*n*=1) and loss to follow up (*n*=43). The 12 month response rate was 75% of the total sample and 84% of those who remained eligible and were sent all questionnaires.

8.3.2. Difference between responders and non-responders

T-tests were conducted to identify any differences between responders and non-responders in baseline data, after removing women who had not responded due to discontinuing tamoxifen and women who were deceased. Non-responders at 3 months were more likely to be non-adherent ($t[30]=2.3$, $p=.026$), had more intense side effects ($t[342]=-2.5$, $p=.014$), and were younger than responders ($t[341]=2.1$, $p=.040$; Table 8.1).

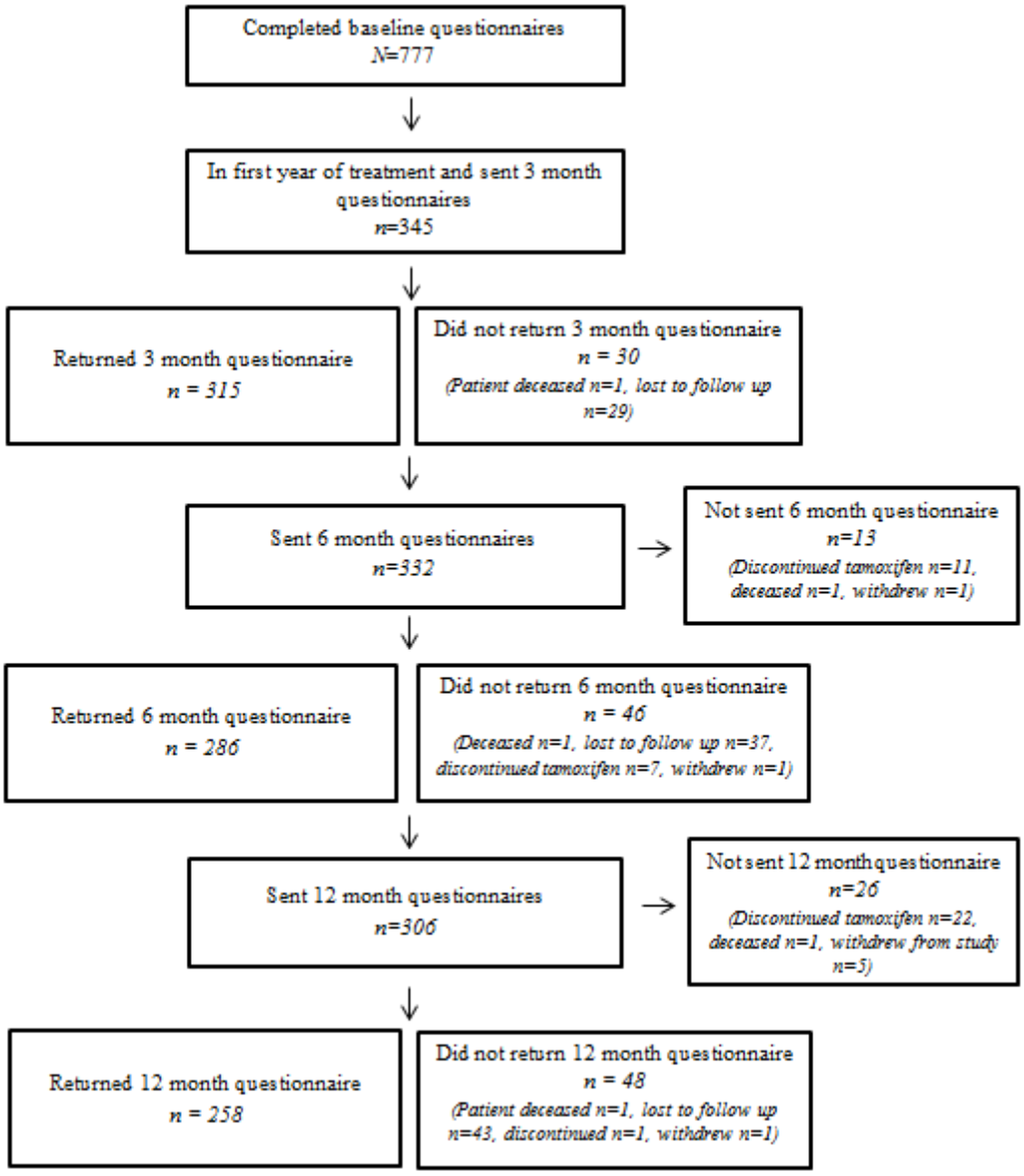

Figure 8.1 Flowchart showing participant retention

At 6 months, non-responders were more likely to be non-adherent (t[41]=2.4, p=.021), had more intense side effects (t[322]=-2.9, p=.004), and had higher baseline distress scores (t[322]=-2.4, p =.015). Non-responders at 6 months were also more likely to be younger (t[321]=3.3, p=.001), to be pre-menopausal (χ^2=5.03, p=.025) and to not be white (χ^2=9.57, p=.002). There were significant differences between responders and non-responders at 12 months for age, ethnicity and menopausal status, with non-responders being younger (t[301]=-3.1, p=.002), more likely to not be white (χ^2=4.04, p=0.44) and more likely to be pre-menopausal (χ^2=4.43, p=.035).

Additional analysis was conducted in order to further explore the association between retention rates and adherence. After removing women who became deceased during the study or who discontinued tamoxifen, women were classified according to how many time points they completed. The majority of women completed all four time points (*n*=222, 64%). The remaining participants completed either the first three time points (*n*=21), the first two time points (*n*=9), only baseline (*n*=20) or they missed several time points across the follow up period (*n*=21). Mean adherence rates over time for each retention pattern are shown in Figure 8.2. Results show that women who completed all four time points had the highest adherence rates, followed by those who completed the first three, then by those who completed the first two questionnaires. Finally, participants who only completed the baseline assessment had the lowest levels of adherence.

8.3.3. Participant demographics

Participant demographics were similar to the demographics of the larger cross-sectional sample in Chapter 6 and are shown in Table 8.2. The majority of participants were white British (95%), had a partner (76%) and were employed (71%). Age ranged from 30 – 90. The mean age was 52 (*SD*=10.3). Participants mostly had Stage I (41%) or Stage II breast cancer (45%) and were premenopausal at diagnosis (55%).

8.3.4. Missing data

Aside from participants missing entire time points, item or scale level missing data was negligible and was all well under 5%. Missing data were therefore replaced using mean imputation. Three participants were missing the Medication Adherence Rating Scale (MARS) at 6 months and four at 12 months, and their previous observations were carried forward.

Table 8.1 Differences between responders and non-responders

	3 months		6 months		12 months	
	Responders (*n*=315)	Non-responders (*n*=29)	Responders (*n*=286)	Non-responders (*n*=38)	Responders (*n*=258)	Non-responders (*n*=46)
Ethnicity (% white)	95%	86%	96%*	84%*	96%*	89%*
Job status (% employed)	71%	73%	70%	79%	72%	68%
Menopausal status (% pre)	55%	55%	53%*	73%*	54%*	71%*
Age *M (SD)*	52.1 (10.2)*	48.0 (10.5)*	52.1 (10.0)*	46.5 (8.5)*	52.0 (9.5)*	47.3 (9.5)*
Months since prescribed tamoxifen *M (SD)*	5.7 (3.8)	6.4 (3.6)	5.8 (3.8)	6.1 (3.9)	5.7 (3.7)	6.4 (4.3)
MARS total *M (SD)*	24.4 (1.4)*	23.3 (2.4)*	24.4 (1.3)*	23.6 (2.1)*	24.5 (1.0)	23.89 (1.9)
Distress *M (SD)*	10.2 (7.1)	12.9 (8.9)	10.0 (6.9)*	12.9 (8.2)*	9.7 (6.8)	11.7 (8.0
Side effect Intensity *M (SD)*	35.2 (11.4)*	40.7 (13.4)*	34.7 (11.0)*	40.4 (13.1)*	34.3 (10.7)	37.9 (13.1)

Note. * indicates a statistically significant difference between responders and non-responders at $p<0.05$. MARS Medication Adherence Rating Scale.

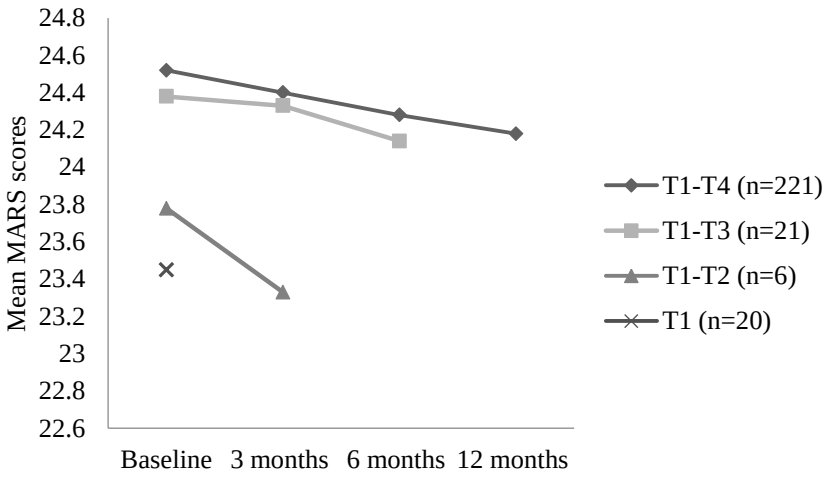

Figure 8.2 Graph showing adherence rates across different patterns of retention

8.3.5. Changes in adherence over time

Scores of 25 on the MARS indicate full adherence, and decreasing scores indicate decreasing rates of adherence. As with the cross-sectional analysis, scores on the MARS were strongly skewed towards overall adherence. Mean MARS scores decreased significantly from 24.37 (*SD*=1.38) at baseline to 24.20 (*SD*=1.57) at 3 months (*t*[314]=2.19, *p*=.029), indicating that people became less adherent (Figure 8.3). Mean MARS scores also significantly decreased between baseline and 6 months (24.06, *SD*=1.77; *t*[284]=4.36, *p*=<.001) and between baseline and 12 months (24.11, *SD*=1.6; *t*[240]=3.95, *p*<.001) (Figure 8.3). Participants were classified as adherent or non-adherent using the same cut offs as the previous cross-sectional study (<25 indicating non-adherence). At baseline, 37% of the sample was non-adherent. This increased to 39% at 3 months, 45% at 6 months and 48% at 12 months

A total score was also calculated for the four MARS items measuring intentional non-adherence only. Scores of 24 indicate full intentional adherence. There were no significant changes between baseline and 3 months, but there was a significant decrease between baseline (23.90, *SD*=0.51) and 6 months (23.70, *SD*=1.27, *t*[273]=2.86, *p*=.005) and between baseline and 12 months (23.69, *SD*=1.32; *t*[240]=-2.73, *p*=.007), indicating that participants became more intentionally non-adherent over time. Women were categorised as intentionally non-adherent if they scored less than 24 on the MARS. Percentages of intentional non-adherence remained stable at 7% between baseline and 3 months. This increased very slightly to 8% at 6 months and 10% at 12 months. One item on the MARS measures unintentional non-adherence, and women were classed as non-adherent if they scored less than 5 on

Table 8.2 Baseline demographic and clinical characteristics of participants

Demographic / clinical characteristics	N (%)
Age	Range 30 – 90, *M*=51.7 (*SD*=10.3)
Ethnicity	
White	325 (95%)
Other	19 (5%)
Age left full time education	Range 14 – 33, *M*=18.0 (*SD*=2.9)
Job status	
Employed	235 (71%)
Not employed	98 (29%)
Relationship status	
With partner	261 (76%)
Not with partner	82 (24%)
Menopausal status at diagnosis	
Premenopausal	175 (55%)
Menopausal/postmenopausal	144 (45%)
Months since prescribed tamoxifen	
< 1 month	28 (8%)
1 - 3 months	70 (20%)
3 – 6 months	93 (27%)
6 – 8 months	47 (14%)
8-12 months	100 (29%)
Stage at diagnosis	
Stage I	138 (41%)
Stage II	153 (45%)
Stage III	39 (11%)
Unsure	11 (3%)
Previous treatment	
Chemotherapy	163 (47%)
Radiotherapy	256 (74%)
Lumpectomy	219 (64%)
Single Mastectomy	115 (33%)
Double Mastectomy	16 (5%)
Hormone receptor status	
Positive	290 (85%)
Negative	4 (1%)
Unsure	46 (13%)
Comorbidities	
0	185 (59%)
1	88 (28%)
2	22 (7%)
3+	17 (6%)

this item. Rates of unintentional non-adherence increased from 35% at baseline to 38% at 3 months, 43% at 6 months and 47% at 12 months (Figure 8.4).

Mean MARS unintentional scores did not change between baseline and 3 months, but there were significant decreases between baseline and 6 months (t[227]=3.17, p=.002), and between baseline and 12 months (t[244]=3.74, p<.001).

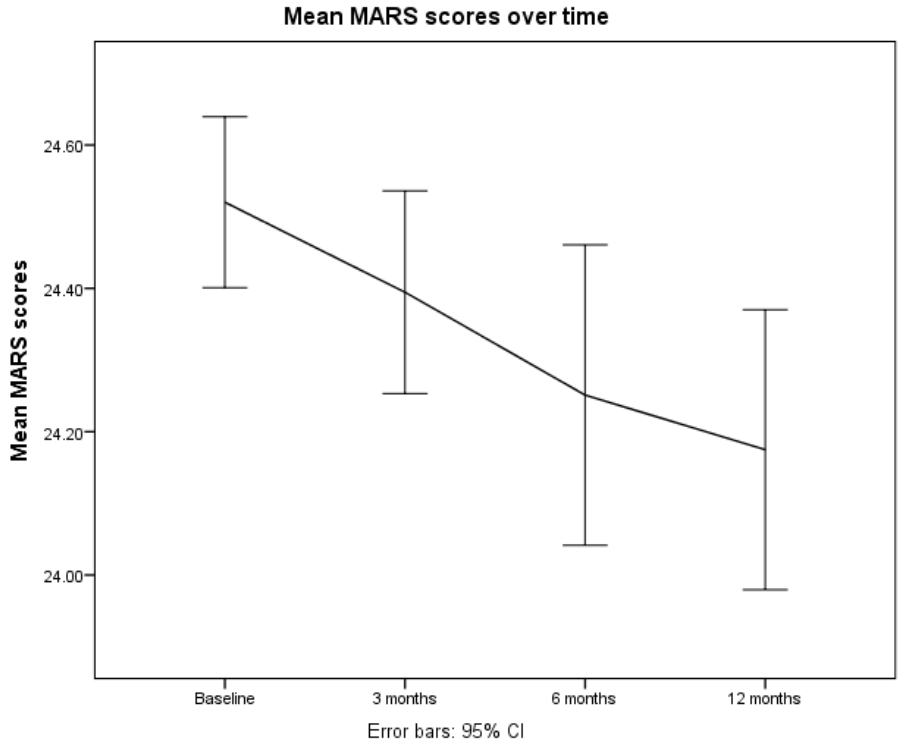

Figure 8.3 Graph showing mean MARS scores from baseline to 12 months

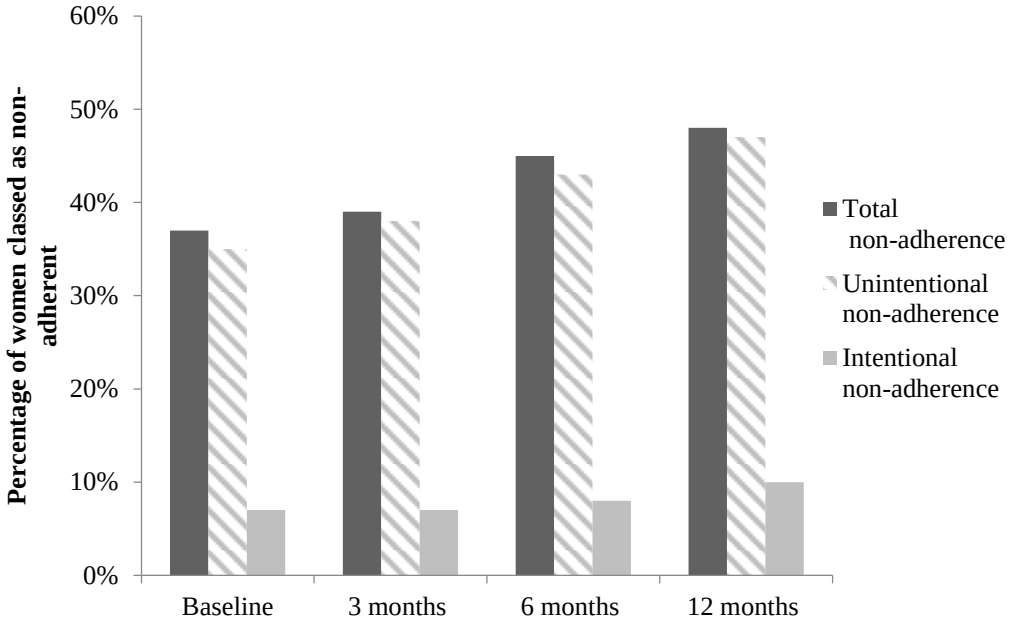

Figure 8.4 Graph showing percentage of women classed as non-adherent over time

Between baseline and 3 months, 6% of participants discontinued, 12% became non-adherent, 8% became adherent and 74% showed no change. Of those who showed no change, 67% were adherent and 33% were non-adherent. Between 3 and 6 months, 5% discontinued, 12% became non-adherent, 6% became adherent and 77% showed no change. Of those who showed no change, 61% were adherent and 39% were non-adherent. Between 6 and 12 months, 5% of participants discontinued, 9% became non-adherent and 7% became adherent. The remaining participants (79%) showed no change in adherence status, of whom 56% were adherent and 44% were non-adherent.

Overall, between baseline and 12 months, 15% discontinued, 16% became non-adherent, 4% became adherent and 65% showed no change in adherence status. In total, 41 patients discontinued tamoxifen over the study period. 23% of these were discontinued by their doctor, 40% were switched to another medication, 20% discussed discontinuing with their doctor and 18% reported making their own choice to discontinue. Similar rates of discontinuation were seen across all three follow up time points.

8.3.6. Changes in psycho-social variables over time

One-way repeated measures ANOVAs were conducted to analyse changes in psychosocial variables over time, using post-hoc tests with Bonferroni correction (Table 8.3). Where the assumption of sphericity was violated, the Hunyh-Feldt or Greenhouse-Geisser corrections were used. Distress

decreased over time, but the effect was not statistically significant (F[2.9,639.6]=2.12, p=.100). Intensity of side effects increased significantly over time (F[2.8, 631.3]=2.37, p<.001). Post-hoc tests indicated significant increases between baseline and 12 months (p<.001). There were no significant changes over time in social support (F[2.9, 651.0]=0.60, p=.613).

8.3.6.1. Common Sense Model of Illness Representations

Figures 8.5-8.6 show changes in illness perceptions over time and Table 8.3 presents the descriptive data and inferential statistics. One-way repeated measures ANOVAs were conducted to analyse changes in these variables. There was a significant effect of time for breast cancer consequences. Post-hoc tests showed that breast cancer consequences decreased significantly between baseline and 12 months (p<.001; Table 8.3). Risk of recurrence beliefs increased slightly over time, but post-hoc tests did not identify any significant differences. Symptoms attributed to tamoxifen (identity) increased significantly over time, with post-hoc tests indicating significant increases between baseline and 3 months (p=.008), baseline and 6 months (p<.001) and baseline and 12 months (p=.002). Beliefs in health behaviours as a cause of recurrence increased significantly over time. Post-hoc tests indicated significant increases between baseline and 3 months (p=.013) and between baseline and 12 months (p=.003). Beliefs in psychological stress as a cause of recurrence also increased significantly over time, with post-hoc tests indicating significant increases between baseline and 3 months (p=.025). There were no significant changes over time for the remaining illness perceptions (treatment control, personal control, coherence, emotional representations, cure and tamoxifen consequences).

Figure 8.7 shows that over time, participants' belief in the necessity of tamoxifen increased, and their concerns about tamoxifen decreased. Therefore, the necessity/concerns differential became more positive over time. Post-hoc tests showed that the necessity/concerns differential increased significantly between baseline (mean=2.94, SD=5.25) and 6 months (mean=4.12, SD=5.17, p<.001) and between baseline and 12 months (mean=4.11, SD=5.38, p=.001).

Table 8.3 Changes to psychosocial variables over time

	Baseline *Mean, SD*	3 months *Mean, SD*	6 months *Mean, SD*	12 months *Mean, SD*	Main effect of time
Distress	9.03 (6.34)	9.41 (6.25)	8.87 (6.56)	8.68 (6.74)	$F(2.9,639.6)=2.12$, $p=.100$
Side effect intensity	1.95 (0.59)***	1.93 (0.61)***	1.97 (0.64)***	2.15 (0.66)***	$F(2.8, 631.3)=2.37$, $p<.001$
Social support	5.89 (1.27)	5.80 (1.27)	5.76 (1.35)	5.83 (1.30)	$F(2.9, 651.0)=0.60$, $p=.613$
Breast cancer consequences	12.07 (3.64)***	11.59 (3.50)***	11.60 (3.58)***	11.14 (3.53)***	$F(3,639) = 6.83$, $p<.001$
Tamoxifen consequences	8.89 (3.62)	9.26 (3.51)	9.42 (3.89)	9.40 (3.80)	$F(2.89,615.7)=2.32$, $p=.077$
Risk of recurrence	10.14 (3.28)*	10.57 (3.11)*	10.39 (3.43)*	10.62 (3.07)*	$F(3,639)=2.99$, $p=.030$
Cure	15.37 (3.25)	15.13 (3.27)	15.37 (3.22)	15.65 (3.10)	$F(2.93,625.6)=2.23$, $p=.085$
Coherence	15.61 (2.77)	15.68 (2.94)	15.56 (3.23)	15.89 (2.94)	$F(4.63,609.6)=1.68$, $p=.174$
Emotional representations	12.91 (4.31)	13.00 (4.18)	12.98 (4.18)	12.66 (4.27)	$F(3,639)=1.08$, $p=.355$
Personal control	13.97 (3.11)	13.90 (2.89)	14.00 (2.98)	14.16 (2.99)	$F(3,639)=0.83$, $p=.479$
Treatment control	15.68 (2.45)	15.46 (2.52)	15.62 (2.32)	15.44 (2.52)	$F(2.93,623.6)=1.26$, $p=.288$
Symptoms attributed to tamoxifen (identity)	4.87 (3.90)***	5.56 (4.28)***	6.01 (4.69)***	5.90 (4.44)***	$F(2.8, 622.1)=61.96$, $p<.001$
Cause: health behaviours	3.25 (0.67)**	3.62 (1.76)**	3.31 (0.74)**	3.40 (0.68)**	$F(1.4,309.6)=12.37$, $p=.005$
Cause: psychological attributions	3.05 (0.92)**	3.29 (1.36)**	3.08 (0.94)**	3.09 (0.93)**	$F(2.2, 489.9)=4.90$, $p=.006$
Concerns	11.79 (4.11)**	11.69 (3.76)**	11.30 (4.06)**	11.18 (3.99)**	$F(2.7,606.0)=4.72$, $p=.004$
Necessity	14.73 (3.60)**	15.23 (3.55)**	15.42 (3.60)**	15.29 (3.62)**	$F(2,9,650.7)=4.01$, $p=.008$
Necessity/concerns differential	2.94 (5.25)***	3.54 (4.92)***	4.12 (5.17)***	4.11 (5.38)***	$F(2.9, 638.0)= 8.49$,$p=<.001$
Intention to take tamoxifen	6.60 (1.06)*	6.75 (0.55)*	6.69 (0.66)*	6.59 (0.83)*	$F(2.3,505.4)=3.34$, $p=.030$
Subjective norm	6.00 (1.11)	5.84 (1.01)	5.84 (1.07)	5.84 (0.99)	$F(2.7,609.5)=2.45$, $p=0.68$
Perceived Behavioural Control	6.26 (1.11)	6.31 (0.83)	6.24 (0.97)	6.28 (0.85)	$F(2.5, 558.7)=0.37$, $p=.740$
Attitude towards tamoxifen	40.59 (7.62)*	39.67 (7.60)*	39.20 (8.05)*	39.17 (7.94)*	$F(3,612)=3.24$, $p=.022$

Note. * Indicates significant main effect of time at $p<0.05$, ** indicates significant main effect of time at $p<0.01$, *** indicates significant main effect of time at $p<0.001$

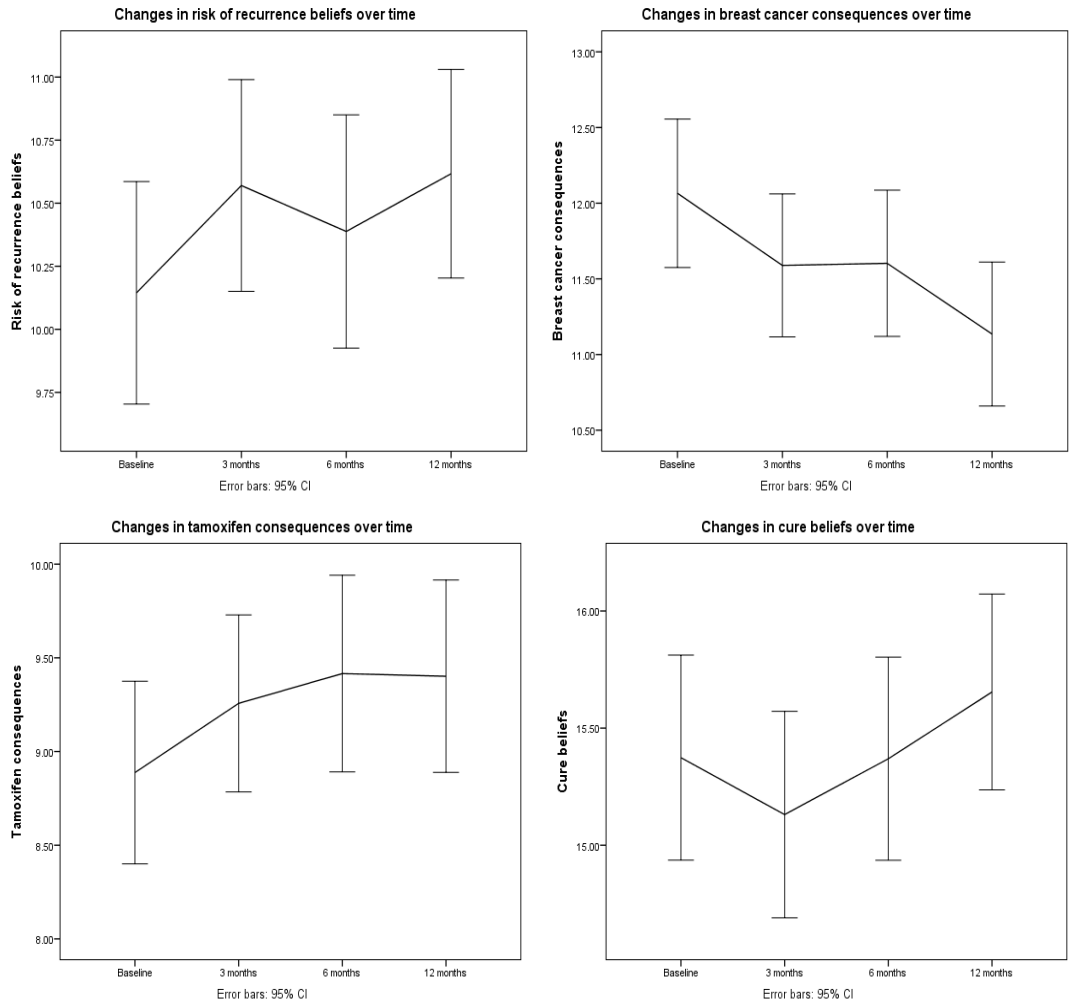

Figure 8.5 Changes in illness perceptions (risk of recurrence, breast cancer consequences, tamoxifen consequences, cure) over time

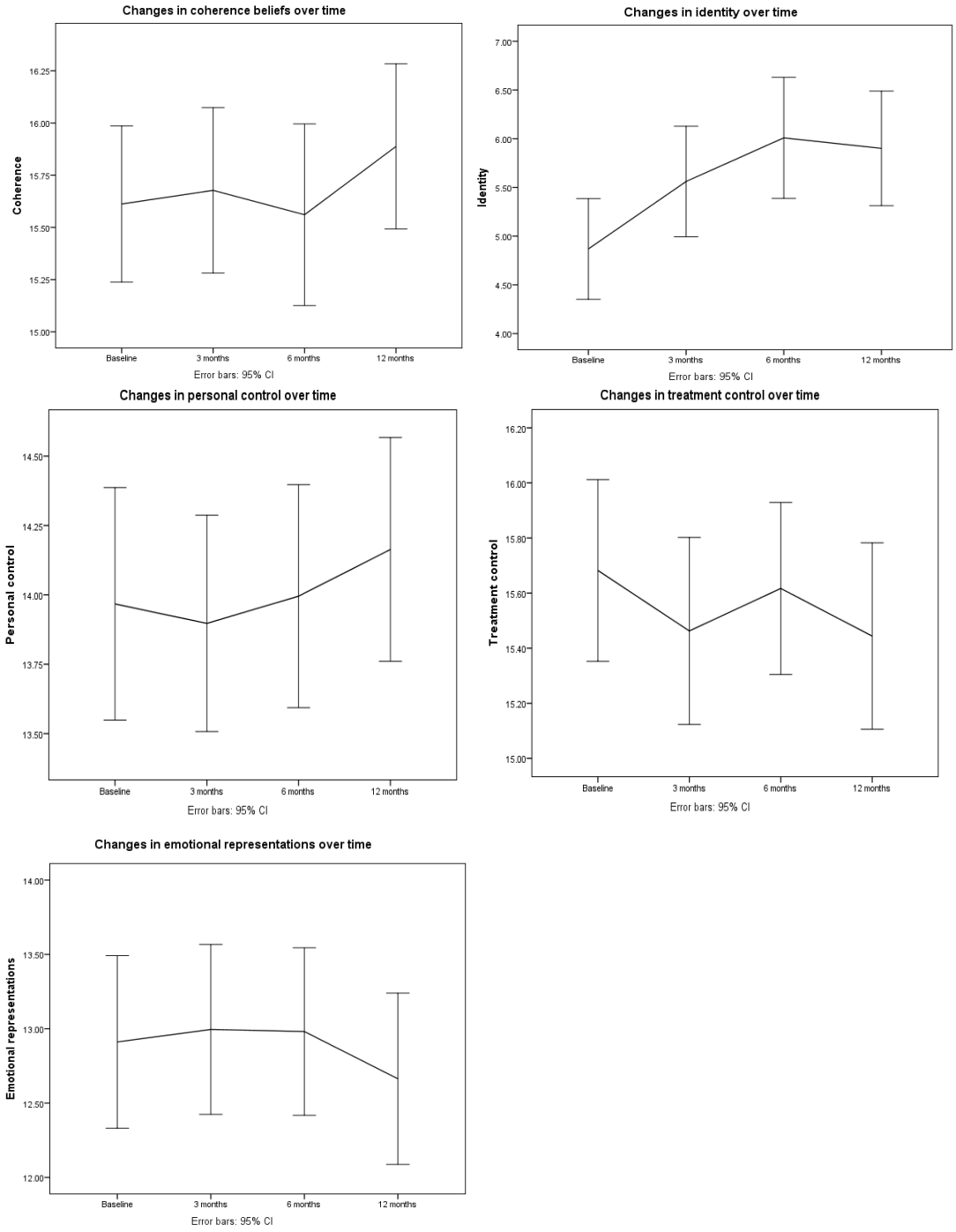

Figure 8.6 Changes in illness perceptions (coherence, identity, personal control, treatment control, emotional representations) over time

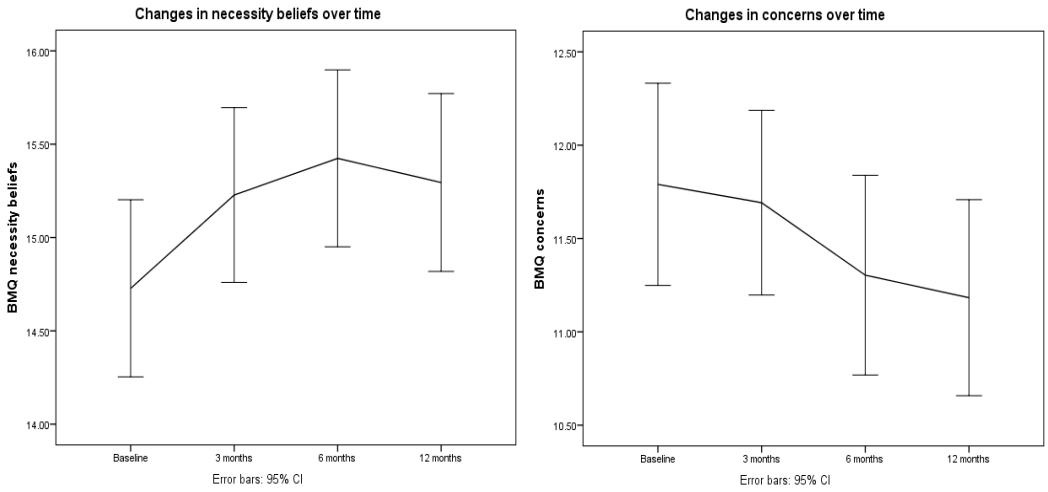

Figure 8.7 Changes in necessity beliefs and concerns over time.

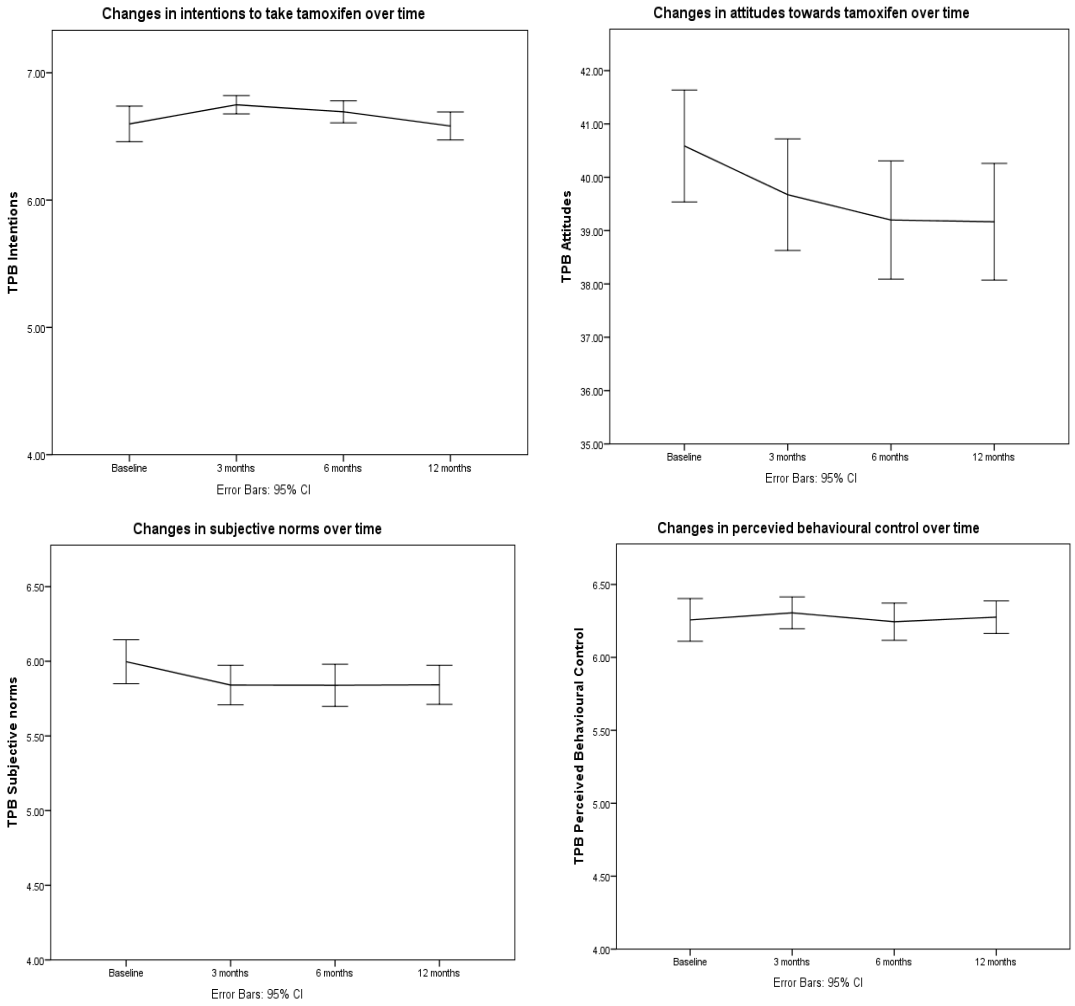

Figure 8.8 Changes in TPB variables over time

8.3.6.1. Theory of Planned Behaviour

The main effect of time for TPB intention to take tamoxifen was significant. Post-hoc tests indicated a significant decrease between 3 and 12 months (p=.008). Attitudes towards tamoxifen became less positive over time. Post-hoc tests indicated significant decreases between baseline and 12 months (p=.043). There was no significant effect of time for subjective norms or for PBC (Figure 8.8).

8.3.7. Latent growth modelling (LGM)

Scores on the MARS were positively skewed which violates the assumptions of the continuous linear LGM. Therefore, instead of the continuous data, the dichotomous non-adherence scores were used to model non-adherence. A univariate LGM was conducted on the non-adherence values to determine if there was any change in non-adherence over time and if this growth followed a linear pattern. This model is shown in Figure 8.9. This basic model was then repeated with the addition of a quadratic function to see if this better represented the change over time.

The loglikelihood and BIC values for the linear and quadratic model are shown in Table 8.4. Results show that the original linear model had superior model fit. This is supported by Figure 8.10 which shows there is more discrepancy between the estimated and observed values in the quadratic model. Furthermore, the quadratic estimate was very small and non-significant, whereas the original linear slope showed a significant effect. There was a significant positive correlation between the intercept and slope (r=0.63, p=.009). The proportion of women classed as non-adherence increased at each time point. There was significant variance in the intercept (7.88, p=.002) but not in the slope (0.09, p=.131).

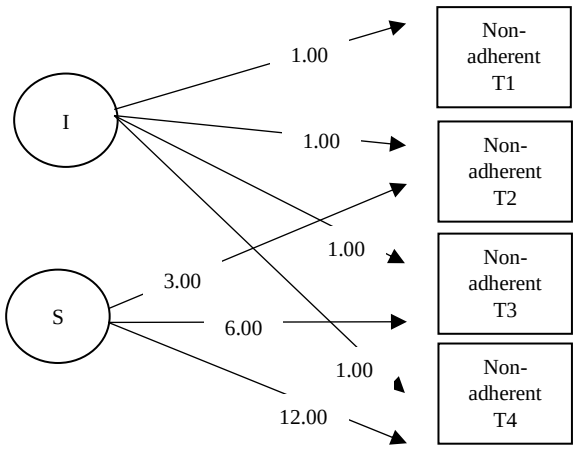

Figure 8.9 Latent growth model for non-adherence scores over time.
Note. I=Intercept. S=Slope.

Table 8.4 Model fit statistics for linear and quadratic models for overall non-adherence

Model	Loglikelihood	BIC	Slope factor	Quadratic factor
Linear	-616.64	1262.49	0.12 (p<.001)	
Quadratic	-614.56	1281.71		0.01 (p=.723)

Note. Lower loglikelihood and BIC values indicate superior model fit.

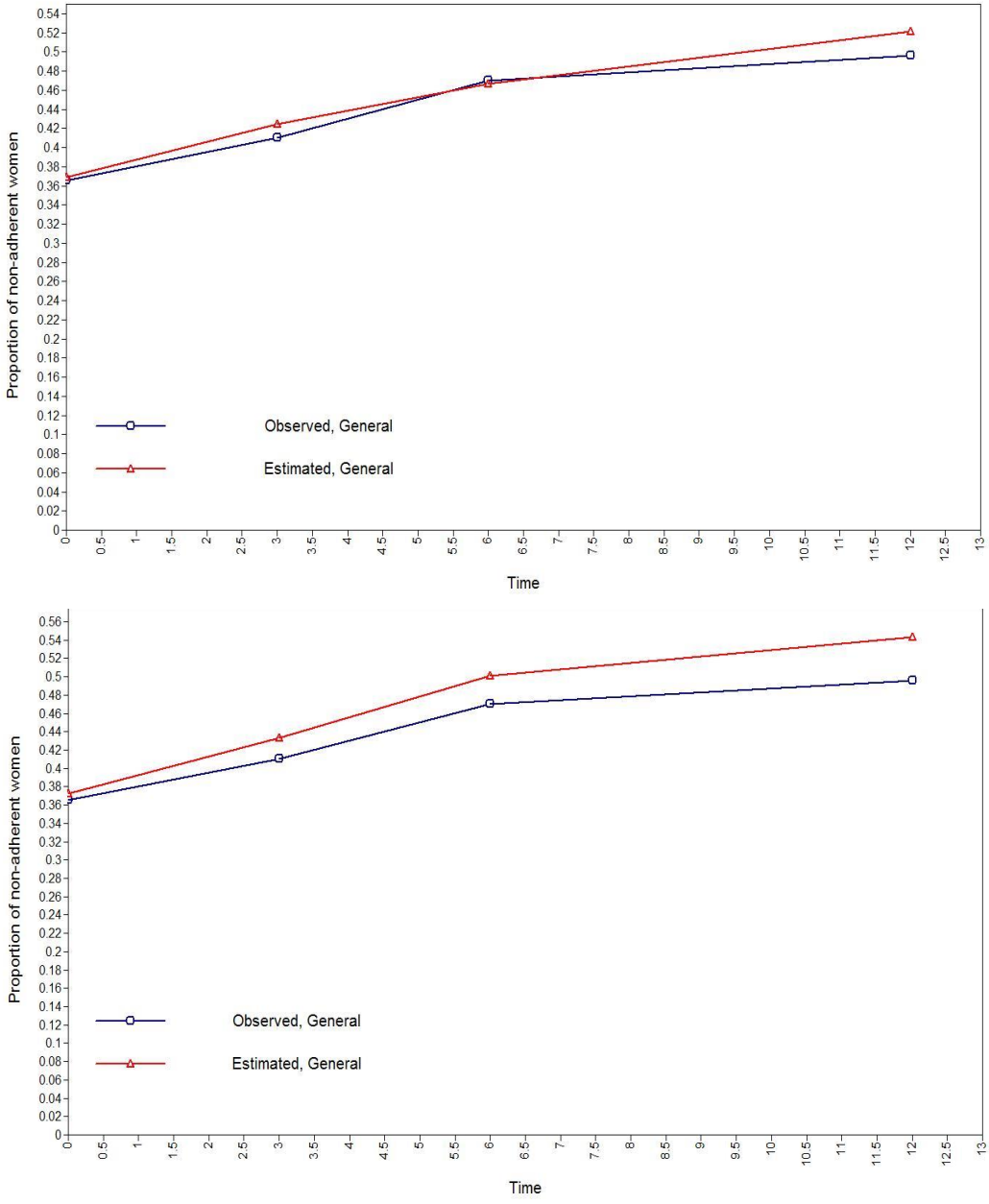

Figure 8.10 Expected and observed values for non-adherence, based on the linear (top graph) and quadratic (bottom graph) models

Once the unconditional LGM was established, baseline covariates were added to the model to identify their effects on the intercept or slope. Potential clinical, demographic and behavioural covariates were chosen based on their correlations with non-adherence (See Appendix F). All CSM and TPB variables were tested in the LGMs. Variables with a significant effect on the intercept or slope at $p \leq .10$ were entered into the final models. Women who were employed, who were younger and who had higher distress scores at baseline had increased odds of non-adherence at the intercept and increased odds of non-adherence over time (Table 8.5). Higher odds of non-adherence at the intercept were also associated with previously having chemotherapy, lower levels of social support and not being white. There was a significant effect of side effects and menopausal status on the slope, with women experiencing more side effects having higher odds of becoming non-adherent over time and women who were post-menopausal at diagnosis having lower risks of becoming non-adherent over time.

In terms of CSM variables, women who had more positive necessity/concerns differentials and who reported fewer tamoxifen consequences at baseline had lower odds of non-adherence at the intercept and lower odds of non-adherence over time. Attributing more symptoms to tamoxifen and believing psychological stress was a cause of recurrence was associated with increased odds of non-adherence. Women who reported higher breast cancer consequences had increased odds of non-adherence over time. From the TPB, more positive attitudes towards tamoxifen, higher subjective norms and PBC were all associated with increased odds of non-adherence. Attitudes and PBC also showed a negative effect on the odds of becoming non-adherent over time.

To test the CSM, variables which were significant predictors of either the intercept or the slope at $p \leq 0.10$ in the bivariate LGMs were entered into a multivariate LGM. Ethnicity was the only factor with a significant effect on the intercept, with women who were not white having nine times higher odds of non-adherence than women who were white (Table 8.6). All other variables showed no significant effects on the intercept. When controlling for other covariates, there were significant effects of the necessity/concern differential and identity on the slope of non-adherence over time. Women with more positive necessity/concern differentials had lower odds of non-adherence over time, as did women who attributed more symptoms to tamoxifen. The effects for job status and distress on the slope of non-adherence neared significance.

Table 8.5 Effects of covariates on the intercept and slope of non-adherence

Variable	Effect on intercept (OR)	Slope	Effect on slope
Ethnicity (black/minority ethnic groups)	9.67 (*p*=.017)	0.11	0.19 (*p*=.326)
Job (employed)	2.33 (*p*=.081)	-0.01	0.18 (*p*=.029)
Menopausal status (post-menopausal)	0.54 (*p*=.187)	0.18	-0.12 (*p*=.095)
Chemotherapy	2.53 (*p*=.030)	0.11	0.03 (*p*=.645)
Age	0.96 (*p*=.077)	0.57	-0.01 (*p*=.035)
Months since prescribed tamoxifen	1.05 (*p*=.388)	0.18	-0.01 (*p*=.289)
Distress	1.05 (*p*=.048)	-0.32	0.02 (*p*=.001)
Social support	0.68 (*p*=.026)	0.37	-0.04 (*p*=.143)
Side effect intensity	1.51 (*p*=.189)	-0.04	0.01 (*p*=.006)
Necessity/concerns differential	0.91 (*p*=.023)	0.18	-0.02 (*p*=.002)
Risk of recurrence	1.01 (*p*=.875)	0.07	0.01 (*p*=.554)
Breast cancer consequences	2.66 (*p*=.281)	-0.16	0.02 (*p*=.023)
Personal control	1.01 (*p*=.912)	0.17	-0.00 (*p*=.820)
Treatment control	1.02 (*p*=.818)	0.52	-0.03 (*p*=.113)
Coherence	0.89 (*p*=.132)	0.33	-0.01 (*p*=.336)
Emotional representations	1.01 (*p*=.824)	-0.04	0.01 (*p*=.123)
Cure	0.95 (*p*=.490)	0.38	-0.02 (*p*=.153)
Tamoxifen consequences	1.13 (*p*=.031)	-0.17	0.03 (*p*=.004)
Cause: health behaviour	1.40 (*p*=.253)	0.23	-0.03 (*p*=.491)
Cause: psychological attributions	1.48 (*p*=.092)	0.12	-0.00 (*p*=.985)
Symptoms attributed to tamoxifen (identity)	1.08 (*p*=.101)	0.09	0.01 (*p*=.414)
Attitude towards tamoxifen	0.93 (*p*=.018)	0.75	-0.02 (*p*=.011)
Subjective Norm	0.72 (*p*=.085)	0.45	-0.06 (*p*=.157)
Perceived Behavioural Control	0.46 (*p*<.001)	0.63	-0.08 (*p*=.072)

Note. All covariates were measured at baseline.

Table 8.6 Results of the multivariate LGM testing variables from the CSM

Variable	Effect on intercept (OR)	Slope	Effect on slope
Model slope		-0.19	
Ethnicity (black/minority ethnic groups)	9.11 (*p*=.035)		-0.00 (*p*=.986)
Job (employed)	2.86 (*p*=.083)		0.18 (*p*=.054)
Menopausal status (post-menopausal)	1.64 (*p*=.416)		-0.11 (*p*=.189)
Age	0.98 (*p*=.621)		0.00 (*p*=.791)
Chemotherapy	2.66 (*p*=.088)		0.01 (*p*=.913)
Distress	1.00 (*p*=.981)		0.01 (*p*=.059)
Social support	0.83 (*p*=.334)		-0.01 (*p*=.803)
Side effect intensity	0.97 (*p*=.398)		0.00 (*p*=.460)
Necessity/concerns differential	0.94 (*p*=.220)		-0.02 (*p*=.006)
Breast cancer consequences	0.92 (*p*=.321)		0.01 (*p*=.546)
Tamoxifen consequences	1.11 (*p*=.210)		0.01 (*p*=.294)
Symptoms attributed to tamoxifen (identity)	1.06 (*p*=.336)		-0.02 (*p*=.043)
Cause: psychological attributions	1.26 (*p*=.384)		-0.06 (*p*=.097)

Note. All covariates were measured at baseline.

The same analysis was run to test the TPB. All three TPB variables were significantly associated with non-adherence at $p \leq 0.10$ so were entered into the multivariate LGM. As with the CSM model, ethnicity was significantly related to the intercept, with women who were non-white having higher odds of non-adherence (Table 8.7). In addition to ethnicity, PBC also showed a significant effect on the intercept, with higher levels of PBC being associated with lower odds of non-adherence. There was a significant effect of distress on the slope. Women who were distressed had higher odds of non-adherence over time.

Table 8.7 Results of the multivariate LGM testing variables from the TPB

Variable	Effect on intercept (OR)	Slope	Effect on slope
Model slope		0.59	
Ethnicity (black/minority ethnic groups)	23.1 (*p*=.010)		-0.09 (*p*=.594)
Job (employed)	2.35 (*p*=.145)		0.11 (*p*=.176)
Menopausal status (post-menopausal)	1.57 (*p*=.425)		-0.11 (*p*=.225)
Chemotherapy	1.85 (*p*=.242)		0.02 (*p*=.824)
Age	0.99 (*p*=.691)		-0.00 (*p*=.802)
Distress	0.97 (*p*=.553)		0.01 (*p*=.048)
Social support	0.70 (*p*=.069)		-0.02 (*p*=.521)
Side effect intensity	0.98 (*p*=. 773)		0.00 (*p*=.993)
Attitude towards tamoxifen	0.97 (*p*=.242)		-0.01 (*p*=.064)
Subjective Norm	1.22 (*p*=.408)		0.01 (*p*=.819)
Perceived Behavioural Control	0.38 (*p*<.001)		-0.05 (*p*=.293)

Note. All covariates were measured at baseline.

8.3.7.1. LGM for intentional non-adherence

As with the cross-sectional study, separate analyses were carried out to identify if there were unique predictors of intentional and unintentional non-adherence. Very few women were categorised as intentionally non-adherent, although this did increase slightly over time (see Figure 8.4). Whilst neither the linear nor the quadratic model provided a good fit for the data (Figure 8.11), the linear model was slightly better (Table 8.8). Whilst the slope factor for this model was not significant, the size of the slope was equivalent to the slope for total non-adherence, representing similar increases in the odds of becoming non-adherent each month. It is likely that the slope factor was non-significant because of the small proportion of women classed as intentionally non-adherent (7-10%). Due to this lack of power, it was unlikely that significant predictors of the slope would be identified.

Table 8.8 Model fit statistics for linear and quadratic models for intentional non-adherence

Model	Loglikelihood	BIC	Slope factor	Quadratic factor
Linear	-270.67	570.55	0.12 (*p*=.514)	
Quadratic	-275.70	604.00		-0.08 (*p*=.258)

Note. Lower loglikelihood and BIC values indicate superior model fit.

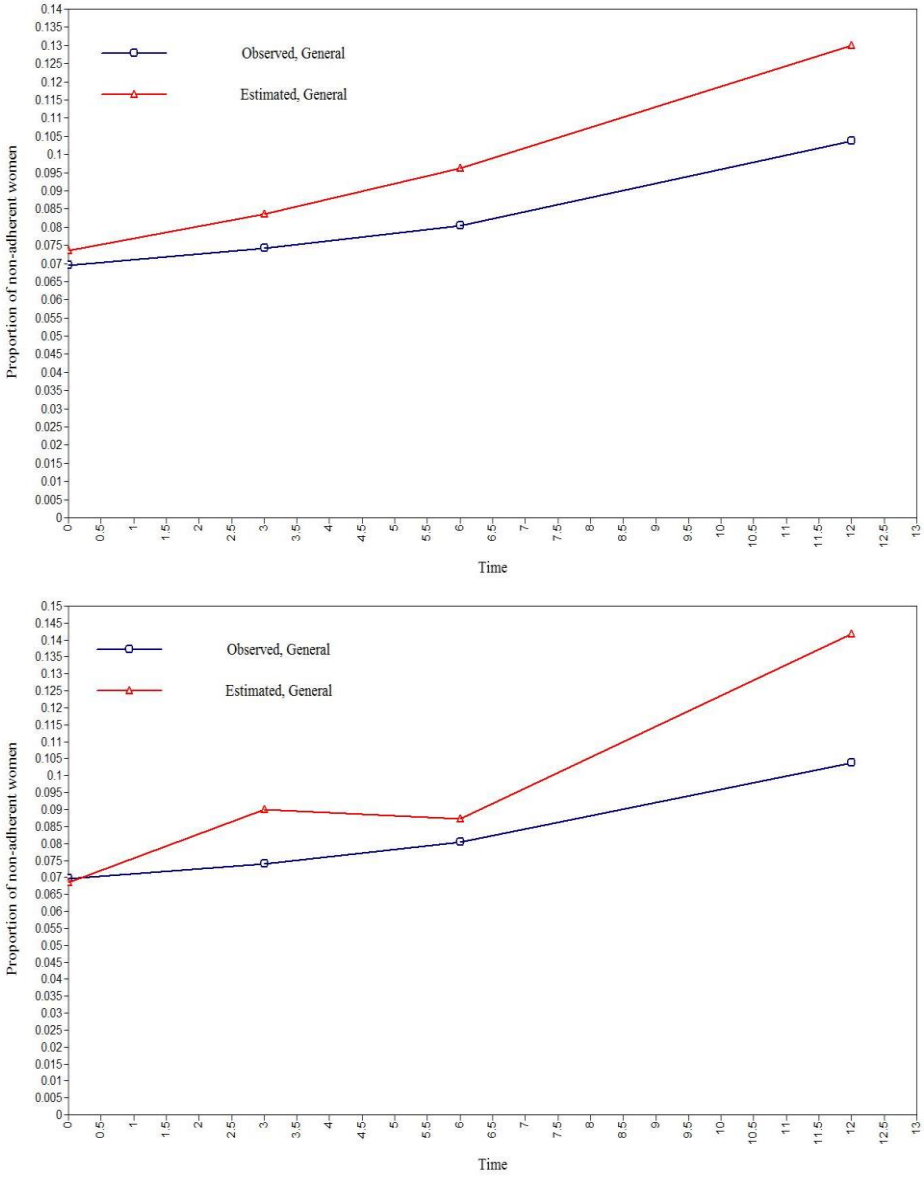

Figure 8.11 Expected and observed values for intentional non-adherence, based on the linear (top graph) and quadratic (bottom graph) models.

In bivariate analyses the following variables were associated with increased odds of non-adherence at the intercept: distress, intensity of side effects, breast cancer consequences, tamoxifen consequences, beliefs in psychological stress as a cause of recurrence and attributing more symptoms to tamoxifen. Social support, higher necessity/concern differentials, higher treatment control beliefs, more positive attitudes towards tamoxifen and higher PBC were associated with decreased odds of non-adherence at the intercept. These variables were entered into multivariate LGMs to test the CSM and TPB. As expected, there were no significant effects on the slope at $p<.05$, but attributing health behaviours as a cause of recurrence showed an effect on the slope at $p<.10$ (Table 8.9).

In the CSM model, the only effect which remained significant when controlling for other variables, was the effect of necessity/concern differential on the intercept, with a 1 point higher score on the differential being associated with 20% lower odds of intentional non-adherence (Table 8.10). In the TPB model, the only effect which remained significant was the effect of PBC on the intercept, with higher PBC being associated with decreased odds of non-adherence (Table 8.11). There were no significant effects for covariates on the slope for intentional non-adherence.

Table 8.9 Effects of covariates on the intercept and slope for intentional non-adherence

Variable	Effect on intercept (OR)	Slope	Effect on slope
Ethnicity (black/minority ethnic groups)	0.70 (*p*=.822)	0.11	0.26 (*p*=.159)
Job (employed)	0.79 (*p*=.770)	0.16	-0.04 (*p*=.580)
Menopausal status (post-menopausal)	2.02 (*p*=.345)	0.18	-0.05 (*p*=.417)
Chemotherapy	1.71 (*p*=.444)	0.14	-0.04 (*p*=.603)
Age	0.99 (*p*=.726)	0.24	-0.00 (*p*=.563)
Months since prescribed tamoxifen	1.14 (*p*=.157)	0.14	-0.01 (*p*=.396)
Distress	1.15 (*p*=.004)	0.07	0.00 (*p*=.832)
Social support	0.63 (*p*=.087)	0.10	0.00 (*p*=.966)
Side effect intensity	1.08 (*p*=.007)	0.14	-0.00 (*p*=.821)
Necessity/concerns differential	0.76 (*p*=.003)	0.10	0.00 (*p*=.714)
Risk of recurrence	0.97 (*p*=.820)	0.14	-0.00 (*p*=.862)
Breast cancer consequences	1.23 (*p*=.080)	0.08	0.00 (*p*=.810)
Personal control	0.97 (*p*=.857)	0.25	-0.01 (*p*=.455)
Treatment control	0.76 (*p*=.097)	0.13	-0.00 (*p*=.953)
Coherence	0.78 (*p*=.235)	-0.14	0.02 (*p*=.235)
Emotional representations	1.04 (*p*=.600)	0.09	0.00 (*p*=.827)
Cure	1.04 (*p*=.752)	0.23	-0.01 (*p*=.527)
Tamoxifen consequences	1.33 (*p*=.012)	0.08	0.00 (*p*=.740)
Cause: health behaviour	0.99 (*p*=.995)	0.43	-0.09 (*p*=.074)
Cause: psychological attributions	2.54 (*p*=.062)	0.30	-0.06 (*p*=.169)
Symptoms attributed to tamoxifen (identity)	1.20 (*p*=.018)	0.14	-0.01 (*p*=.605)
Attitude towards tamoxifen	0.87 (*p*=.006)	-0.17	0.01 (*p*=.255)
Subjective Norm	0.73 (*p*=.288)	0.22	-0.02 (*p*=.633)
Perceived Behavioural Control	0.30 (*p*<.001)	0.05	0.01 (*p*=.749)

Note. All covariates were measured at baseline.

Table 8.10 Results of the multivariate LGM testing variables from the CSM: Intentional non-adherence

Variable	Effect on intercept (OR)	Slope	Effect on slope
Model slope		0.28	
Distress	1.08 (*p*=.251)		0.00 (*p*=.866)
Social support	1.00 (*p*=.993)		0.00 (*p*=.877)
Side effect intensity	1.00 (*p*=.977)		-0.00 (*p*=.538)
Necessity/concerns differential	0.81 (*p*=.020)		0.01 (*p*=.452)
Tamoxifen consequences	1.06 (*p*=.662)		0.02 (*p*=.188)
Breast cancer consequences	0.91 (*p*=.462)		0.01 (*p*=.474)
Symptoms attributed to tamoxifen (identity)	1.08 (*p*=.389)		-0.01 (*p*=.363)
Treatment control	1.03 (*p*=.859)		0.00 (*p*=.967)
Cause: health behaviour	0.63 (*p*=.385)		-0.09 (*p*=.179)
Cause: psychological attributions	1.81 (*p*=.228)		-0.05 (*p*=.337)

Note. All covariates were measured at baseline.

Table 8.11 Results of the multivariate LGM testing variables from the TPB: Intentional non-adherence

Variable	Effect on intercept (OR)	Slope	Effect on slope
Model slope		0.01	
Distress	1.08 (*p*=.197)		-0.00 (*p*=.942)
Social support	0.99 (*p*=.429)		-0.01 (*p*=.726)
Side effect intensity	1.01 (*p*=.788)		-0.00 (*p*=.839)
Perceived Behavioural Control	0.36 (*p*=.002)		-0.01 (*p*=.883)
Attitude towards tamoxifen	0.95 (*p*=.221)		0.01 (*p*=.358)

Note. All covariates were measured at baseline.

8.3.7.2. LGM for unintentional non-adherence

The results of the univariate LGM for unintentional non-adherence are shown in Table 8.12. Results show that the linear model provided superior model fit, which is supported by the expected and observed values shown in Figure 8.12. The slope factor was significant and represents a significant increase in the odds of non-adherence per month.

The following variables were associated with increased odds of non-adherence at the intercept: being non-white, being employed and having had chemotherapy. The following variables were associated with decreased odds of non-adherence at the intercept: being older, higher levels of social support, higher necessity/concerns differential, more positive attitudes towards tamoxifen, stronger subjective norms and higher PBC.

Table 8.12 Model fit statistics for linear and quadratic models for unintentional non-adherence

Model	Loglikelihood	BIC	Slope factor	Quadratic factor
Linear	-592.11	1213.44	0.11, *p*<.001	
Quadratic	-590.90	1234.39		0.00, *p*=.916

Note. Lower loglikelihood and BIC values indicate superior model fit.

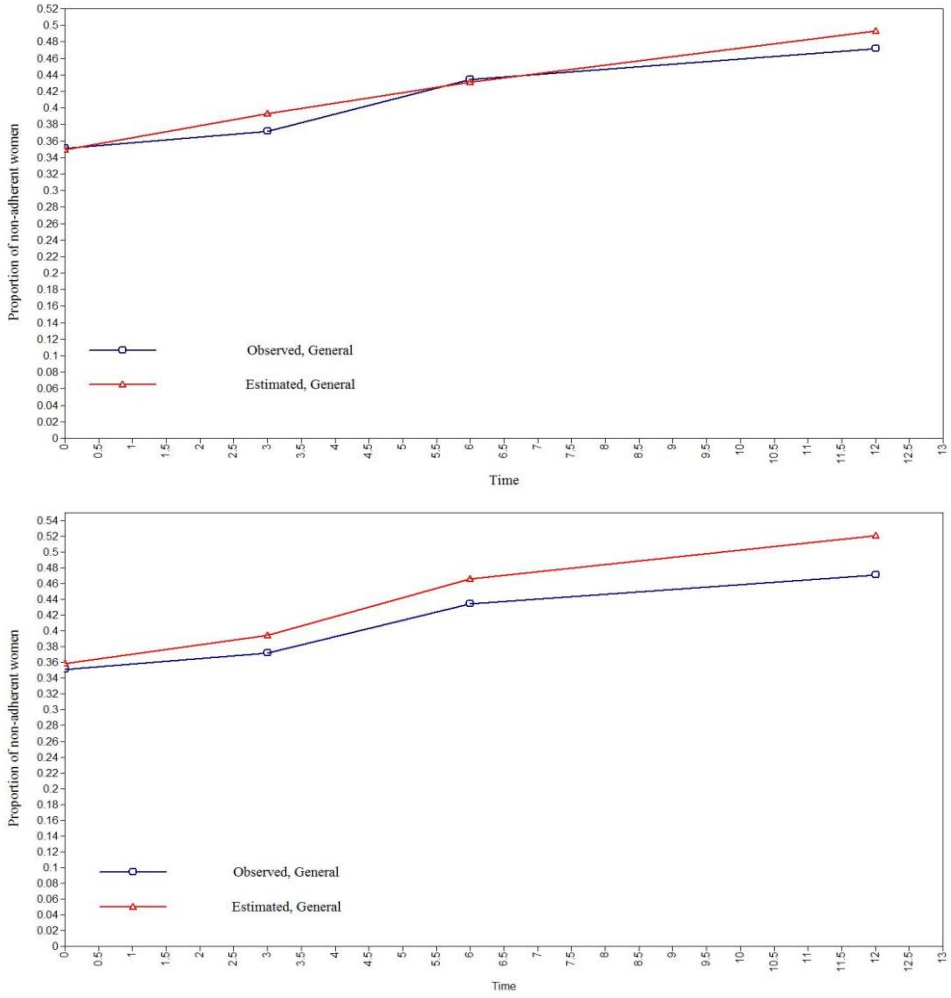

Figure 8.12 Expected and observed values for unintentional non-adherence, based on the linear (top graph) and quadratic (bottom graph) models.

Higher scores on the distress scale were associated with increased odds of becoming non-adherent over time, as were experiencing more side effects and higher breast cancer and tamoxifen consequences. Having a positive necessity/concerns differential and more positive attitudes towards tamoxifen were associated with lower odds of becoming non-adherent over time (Table 8.13).

These variables were then entered into models to test the CSM and TPB models. In the CSM model, ethnicity and job status were significantly related to the intercept, with women from minority ethnic groups and women who were employed having higher odds of non-adherence (Table 8.14). Necessity/concerns differential was associated with the slope of non-adherence, with less positive differentials being associated with increased odds of non-adherence over time. In the TPB model, there was a significant effect of ethnicity on the intercept, with women from minority ethnic groups having increased odds of non-adherence.

Higher levels of PBC were associated with increased odds of non-adherence at the intercept but not over time.

Table 8.13 Effects of covariates on the intercept and slope for unintentional non-adherence

Variable	Effect on intercept (OR)	Slope	Effect on slope
Ethnicity (black/minority ethnic groups)	11.65 (*p*=.015)	0.11	0.02 (*p*=.874)
Job (employed)	3.79 (*p*=.019)	0.04	0.09 (*p*=.257)
Menopausal status (post-menopausal)	0.47 (*p*=.156)	0.16	-0.10 (*p*=.144)
Age	0.46 (*p*=.027)	0.37	-0.01 (*p*=.205)
Chemotherapy	2.65 (*p*=.040)	0.10	0.02 (*p*=.751)
Distress	1.04 (*p*=.220)	-0.18	0.01 (*p*=.013)
Social support	0.66 (*p*=.025)	0.24	-0.02 (*p*=.357)
Side effect intensity	1.02 (*p*=.412)	-0.01	0.01 (*p*=.011)
Necessity/concerns differential	0.92 (*p*=.076)	0.15	-0.02 (*p*=.014)
Recurrence	1.03 (*p*=.690)	0.07	0.01 (*p*=.571)
Breast cancer consequences	1.10 (*p*=.182)	-0.07	0.02 (*p*=.087)
Personal control	1.00 (*p*=.964)	0.08	0.00 (*p*=.734)
Treatment control	1.01 (*p*=.940)	0.36	-0.02 (*p*=.276)
Coherence	0.88 (*p*=.141)	0.17	-0.00 (*p*=.821)
Emotional representations	1.05 (*p*=.443)	0.00	0.01 (*p*=.227)
Tamoxifen consequences	1.09 (*p*=.166)	-0.07	0.02 (*p*=.017)
Cause: psychological attributions	1.37 (*p*=.224)	0.14	-0.01 (*p*=.728)
Cause: health behaviours	1.50 (*p*=.227)	0.16	-0.02 (*p*=.679)
Symptoms attributed to tamoxifen (identity)	1.05 (*p*=.287)	0.09	0.01 (*p*=.381)
Attitude towards tamoxifen	0.94 (*p*=.061)	0.53	-0.01 (*p*=.041)
Subjective norms	0.67 (*p*=.092)	0.34	-0.04 (*p*=.342)
Perceived Behavioural Control	0.52 (*p*=.005)	0.43	-0.05 (*p*=.212)

Note. All covariates were measured at baseline.

Table 8.14 Results of the multivariate LGM testing variables from the CSM: Unintentional non-adherence

Variable	Effect on intercept (OR)	Slope	Effect on slope
Model slope		-0.08	
Ethnicity (black/minority ethnic group)	11.76 (*p*=.017)		-0.11 (*p*=.375)
Job status (employed)	4.06 (*p*=.037)		0.08 (*p*=.373)
Age	0.99 (*p*=.818)		-0.00 (*p*=.614)
Chemotherapy	2.07 (*p*=.206)		-0.01(*p*=.864)
Distress	1.02 (*p*=.682)		0.01 (*p*=.178)
Social support	0.75 (*p*=.155)		0.01 (*p*=.794)
Side effect intensity	0.98 (*p*=.549)		0.00 (*p*=.666)
Necessity/concerns differential	0.94 (*p*=.207)		-0.01 (*p*=.045)
Tamoxifen consequences	1.03 (*p*=.737)		0.00 (*p*=.721)
Breast cancer consequences	1.00 (*p*=.982)		0.00 (*p*=.979)

Note. All covariates were measured at baseline.

Table 8.15 Results of the multivariate LGM testing variables from the TPB: Unintentional non-adherence

Variable	Effect on intercept (OR)	Slope	Effect on slope
Model slope		0.50	
Ethnicity (black/minority ethnic group)	27.38 (*p*=.004)		-0.15 (*p*=.248)
Job (employed)	3.01 (*p*=.084)		0.06 (*p*=.451)
Age	1.00 (*p*=.841)		-0.01 (*p*=.244)
Chemotherapy	0.99 (*p*=.419)		-0.01 (*p*=.864)
Distress	1.01 (*p*=.811)		0.01 (*p*=.127)
Social support	0.71 (*p*=.074)		-0.00 (*p*=.976)
Side effect intensity	0.97 (*p*=.302)		0.00 (*p*=.877)
Attitude towards tamoxifen	0.97 (*p*=.391)		-0.01 (*p*=.074)
Subjective norms	1.07 (*p*=.798)		0.00 (*p*=.998)
Perceived Behavioural Control	0.51 (*p*=.011)		-0.03 (*p*=.074)

Note. All covariates were measured at baseline.

8.3.8. Model fit

The predictive probabilities from the CSM and TPB models for total non-adherence (Table 8.6/8.7) were exported into Stata in order to conduct ROC analyses. The analysis tested the ability of both models to discriminate between adherent and non-adherent participants. The ROC area indicates the predictive ability of each model. Table 8.16 shows the results for each time point and for the overall assessment. Both models provided excellent ability to discriminate between adherent and non-adherent participants, with very high values for the ROC area (0.96-0.99). The accuracies of the CSM and the TPB were very similar, suggesting both models were able to discriminate well between adherent and non-adherent participants. A separate analysis was conducted which ignored the time trend, to see how important the time trend was to predictive accuracy. Results showed this reduced the predictive accuracies of the models, suggesting that the time trend is important to the predictive accuracies shown below.

Table 8.16 ROC analyses to compare predictive ability of CSM and TPB

	CSM ROC area (95% CI)	TPB ROC area (95% CI)
Baseline	0.96 (0.95-0.98)	0.96 (0.94-0.98)
3 months	0.97 (0.95-0.99)	0.97 (0.96-0.99)
6 months	0.98 (0.97-0.99)	0.99 (0.97-1.00)
12 months	0.98 (0.97-0.99)	0.98 (0.97-1.00)
Overall	0.98 (0.96-0.98)	0.97 (0.97-0.98)
Overall, with time trend removed	0.74 (0.70-0.77)	0.76 (0.74-0.81)

8.3.9. Sensitivity analysis for cut-offs on the MARS

There are no set guidelines as to the cut-offs for categorising women as non-adherent on the MARS. Previous studies have used a range of different cut-offs, with the majority using the <25 used in the present study (Huther et al., 2013; Timmers et al., 2014; Timmers et al., 2016; van der Laan et al., 2017). This high cut-off is recommended as it helps to overcome social desirability bias by including all reports of non-adherence (Huther et al., 2013). However, other studies have used more stringent cut off points of <23 (van den Bemt et al., 2009; Zwikker, van Dulmen, den Broeder, van den Bemt & van den Ende, 2014c) or <20 (Ediger et al., 2007). In order to examine whether results would differ if a more stringent cut off was used, a sensitivity analysis was run using a cut off on the MARS of <24. Using these new cut offs, non-adherence rates increased from 14% at baseline to 23% at 12 months, replicating the pattern of increases shown in the main analysis (See Appendix G). LGMs to test individual predictors, as well as the CSM and TPB were also run, showing a similar pattern of results to the main analyses (see Appendix G). However, whilst ethnicity and job status were significant predictors of non-adherence in the main analysis, this was not replicated in the sensitivity analysis. In addition, menopausal status was a significant predictor of non-adherence in the sensitivity analysis (effect on slope: -0.212, p=.023), but this was not shown in the main analysis. Similar results were found for the effects of distress, social support and side effects on non-adherence. In terms of the model variables, attitudes, PBC, necessity/concerns differential, identity, breast cancer consequences and tamoxifen consequences were significant bivariate predictors in both sets of analyses. Coherence beliefs had a significant effect on the intercept of non-adherence in the sensitivity analysis (OR=0.78, p=.006), an effect which was not found in the main analyses. The multivariate analyses testing the CSM and TPB showed very similar results to the main analysis. The necessity/concerns differential and identity remained significant predictors of non-adherence when controlling for other variables, as found in the main analyses. However, in the sensitivity analyses, tamoxifen consequences also remained a significant predictor of increased non-adherence (0.05, p=.018). The sensitivity analyses also replicated the effects shown in the main analyses for TPB variables.

8.4. Discussion

This was one of the first studies to use a longitudinal design to identify psychosocial predictors of tamoxifen non-adherence. Results showed that 37% of women in their first year of treatment reported being non-adherent, and that these reports increased significantly over the one year follow up period. Several predictors of non-adherence were identified, the most consistent being from minority ethnic groups, having lower necessity/concern

differentials, and lower PBC. These results provide important information to help support women taking tamoxifen.

As hypothesised, results showed that reported non-adherence rates increased significantly over time, even across this relatively short follow up period. This is in line with previous studies showing increases in tamoxifen non-adherence rates over time (Partridge et al., 2003; Seneviratne et al., 2015; Wu et al., 2012). The proportion of non-adherent women was high, reinforcing the need to intervene to support these women. Furthermore, the true incidence of non-adherence is likely higher than the rates reported here, as non-adherent women were less likely to return their follow up questionnaires at each time point. It is also likely that non-adherent women would be less likely to consent to take part in the study. There may also be issues with the MARS failing to correctly identify non-adherent participants. Self-report measures of adherence often have weak sensitivity for identifying non-adherence (Lam & Fresco, 2015; Stirratt et al., 2015).

Only 41 participants (12%) discontinued tamoxifen during the study period. This is much lower than previous estimates of 40-50% (Hadji et al., 2013b; Makubate et al., 2013; McCowan et al., 2008; Owusu et al., 2008). Furthermore, whilst 12% discontinued over the study period, only seven of these reported making their own choice to discontinue treatment and eight reported making a joint decision with their doctor. The remaining participants were either discontinued by their doctor or switched to another medication. This represents a very low proportion of patients who have reported making a deliberate and volitional decision to discontinue treatment. There are three potential reasons these discontinuation rates may be lower than those seen in previous studies. Firstly, these rates are only across a twelve month period and only show women in their first 2 years of treatment. Higher discontinuation rates may be seen if patients were followed up for a longer period. However, comparable studies have shown that 22-39% of women discontinued within the first 2 years (Brito et al., 2014b; Huiart et al., 2012; Kostev et al., 2013; Nekhylvdov et al., 2011; van Herk-Sukel et al., 2010), which is still considerably higher than the current rates. However, as discussed in Chapter 2, the majority of previous studies fail to differentiate why someone may become non-persistent. Therefore, another reason the previous studies report higher discontinuation rates is that they likely include women who have been discontinued by their doctor or who have been switched to another medication, and they may not represent accurate rates of women who have decided to discontinue treatment. Finally, this study used self-report measures and women may not feel comfortable admitting that they have completely stopped their medication. Objective measures such as prescription refill rates may have provided higher rates of non-persistence. Due to the low rates of non-persistence in this study, it was not possible to identify potential predictors of non-persistence

specifically. Instead, women who made a deliberate decision to discontinue were categorised as non-adherent for the purpose of analysis. Future research should investigate if there are distinct determinants of non-adherence or non-persistence.

Contrary to what is often suggested clinically to patients, side effects did not abate over time. Instead, reported intensity of side effects increased significantly over the 12 month period. This supports the analysis shown in Chapter 7 and suggests that side effects do not actually diminish over time or that women do not appear to be getting better at managing their symptoms over time. There is therefore a need to support women with their side effects, both at the beginning of treatment and across the treatment trajectory, in order to improve quality of life in these patients. This has implications for the intervention development, and suggests that side effect management should be something offered to all women, not just women in the beginning of treatment. It may also be important to give women more accurate expectations of how long the side effects may last.

There were some changes over time to illness and medication beliefs. Risk of recurrence beliefs increased significantly, but these changes were small. Identity, beliefs in psychological stress as a cause of recurrence and beliefs in health behaviours as a cause of recurrence also increased over time. This supports previous research showing changes in illness perceptions over time (Bijsterbosch et al., 2009; Dempster et al., 2011) and provides some support for the proposed self-regulatory nature of the CSM. The fact that risk of recurrence beliefs changed over time is contrary to what would be expected, but these changes are small and could be an artefact of repeated measurement. Women attributed more symptoms to tamoxifen over time, which may be of interest clinically, as it may cause women to feel more negatively about the drug. However, negative perceptions or attitudes towards tamoxifen did not increase in this study. As hypothesised, tamoxifen consequences remained stable. The set of changes shown in this study does not reflect changes to perceptions seen in other conditions. However, this lack of consistency makes theoretical sense, as every condition has a distinct illness trajectory (Bonsaksen, Lerdal & Fagermoen, 2015). The CSM assumes that illness representations will be shaped by the appraisal of coping strategies, such as adherence (Leventhal et al., 1992). However, unless BCS experience a recurrence, there is no physiological feedback from tamoxifen adherence or non-adherence. Therefore, the success or failure of this coping strategy will not necessarily influence their illness perceptions. This may account for the stable nature of the majority of illness perceptions in this study.

Necessity beliefs increased over time, which contrasts with a previous study showing that perceived necessity for immunosuppressants decreased over time in kidney transplant

patients (Massey et al., 2015). Concerns also decreased over time, and the necessity/concerns differential became more positive, suggesting that women begin to weigh their beliefs up more positively over time. However, the changes in necessity and concern beliefs were relatively small and may not represent clinically relevant changes. Very little research has investigated the dynamic nature of the TPB, and the model lacks the self-regulatory component of the CSM. However, the results of this study show that there are some changes to TPB constructs. Attitudes towards tamoxifen became less positive over time and there were very small decreases in intention to take tamoxifen over time.

Increased non-adherence was seen in women from minority ethnic groups, with up to 27 times increased odds of non-adherence when controlling for other covariates. This is an important finding as studies have shown that women from minority ethnic groups tend to show poorer clinical outcomes in breast cancer than white women (Chlebowski et al., 2005; Clegg et al., 2002; Eley et al., 1994). Potential explanations for this include socioeconomic status, lack of engagement in screening and treatment or biological differences (Carey et al., 2006). These results suggest that higher rates of non-adherence may contribute to the poorer clinical outcomes seen in women from minority ethnic groups. The systematic review in Chapter 3 showed an inconsistent relationship between race and non-adherence, but there was some evidence to suggest that black women were more likely to be non-adherent than white women. Furthermore, a recent review has supported the relationship between HT non-adherence and race (Roberts, Wheeler & Reeder-Hayes, 2015). Therefore, there is a need to investigate this relationship further and to identify ways to support women from minority ethnic groups with their treatment. The fact that ethnicity was related specifically to unintentional but not intentional non-adherence provides potential avenues for intervention. There may be a need to support these women with remembering to take their medication every day and developing a structured medication taking routine. However, the proportion of women from minority ethnic groups was very small and the results should be interpreted with caution.

Women who were employed had up to four times higher odds of unintentional non-adherence. Whilst the systematic review in Chapter 3 showed no consistent effects for employment status on adherence, several recent studies have supported the current findings, showing an association between being employed and higher HT non-adherence (Brett et al., 2016; Quinn et al., 2016). This might be related to the fact that women who are employed are more likely to be younger, but effects remained significant when controlling for age. However, women in the qualitative study in Chapter 4 discussed difficulties with working when experiencing side effects such as hot flushes or fatigue. Therefore, this increase in non-adherence for women who are working may be a result of difficulties managing side

effects in the workplace. Job status was related to non-adherence in the analysis for total non-adherence and for unintentional non-adherence, which may suggest that working women are more likely to forget their medication. Activities around goal and routine setting may help these women to remember to take tamoxifen whilst at work and at home. Other predictors of non-adherence include distress, with higher distress scores at baseline being associated with increased odds of non-adherence over time. This supports the studies in the systematic review showing a positive relationship between depression and HT non-adherence. Results suggest that intervening to improve distress in this population may help to improve adherence rates. Social support was also identified as a potential target for intervention, as low social support was associated with increased odds of non-adherence.

More intense side effects at baseline were associated with increased odds of non-adherence over time, consistent with several studies showing that side effects are a key reason women discontinue treatment (Grunfeld et al., 2005; Moon et al., 2017b; Wells et al., 2016). This is also in line with the qualitative findings that experience of side effects contributes to women becoming non-adherent or non-persistent (Chapter 4). These results suggest that intervening to improve management of side effects may help to improve adherence rates. This is particularly important as several studies have shown that tamoxifen side effects may be an indication of treatment success (Cuzick et al., 2008; Fontein et al., 2013; Mortimer et al., 2008). Interestingly, side effects were associated with increased odds of non-adherence over time, but not at the intercept, suggesting that side effects may have more of a delayed impact on non-adherence. Again, this is in keeping with the qualitative analyses which showed that women weigh up their side effects against their beliefs. It may be that this weighing up process causes a knock on effect on later non-adherence, rather than immediately causing women not to adhere. However, as with the cross-sectional analyses, the effect of side effects on adherence did not remain significant when controlling for the CSM or TPB variables. This suggests that these psychological variables might contribute to the relationship between side effects and non-adherence. Many researchers and clinicians assume that side effects are the main driver of non-adherence, but this research suggests that it may be more important to consider these psychological variables alongside side effects.

Both the CSM and the TPB provided useful explanation of non-adherence, supporting the results found in the cross-sectional analyses. The ROC analyses showed that both models provided excellent discrimination of adherent and non-adherent women. This supports the utility of these models and further highlights their use in their intervention development. However, whilst the discriminative abilities of both models were very high (0.96-0.99), this reduced to 0.74-0.76 when the time trend was removed. This suggests that the inclusion of previous adherence behaviour may have been accounting for the very high scores in the

ROC analysis. Nonetheless, results show good predictive ability even when the time trend was removed, and the results were comparable across the TPB and the CSM. These results also have theoretical implications, by suggesting that whilst these are distinct theories, both are equally as effective at predicting non-adherence. Chapter 6 suggested that the models were complemented well by each other, a finding which is supported here, as constructs from both models appear to be important in understanding non-adherence. Combining the key constructs from both models to create a more parsimonious model may provide superior prediction of medication adherence in future studies. Future research should investigate if this is also the case in the prediction of other health behaviours. Any interventions to improve adherence may also benefit from combining elements from both theories, rather than focussing solely on one model.

As hypothesised, the necessity/concerns differential at baseline was associated with increased odds of initial non-adherence and increased odds of non-adherence over time. The differential remained significant in all analyses when controlling for other covariates. This highlights the importance of medication beliefs in understanding tamoxifen adherence and intervening to improve adherence. The importance of this variable has also been shown in the analysis presented in Chapter 3, Chapter 4 and Chapter 6, as well as in other research in HT non-adherence (Brett et al., 2016; Fink et al., 2004). Other illness perceptions were also related to non-adherence, such as tamoxifen consequences and beliefs that psychological stress caused a recurrence, but these did not remain significant in the multivariate analyses. However, these results suggest that establishing more accurate perceptions around risk of recurrence and reducing the impact of side effects may improve adherence. Attributing more symptoms to tamoxifen (higher tamoxifen identity) was associated with lower odds of non-adherence over time for the total adherence analysis, and increased odds of non-adherence in the analysis for intentional non-adherence. This discrepancy is likely due to the fact that the analysis for total non-adherence is made up mainly of unintentionally non-adherent women, for whom tamoxifen identity is not a significant predictor. This therefore likely reduces the effects of tamoxifen identity in the combined total adherence model.

Variables from the TPB also helped explain non-adherence. More positive attitudes to tamoxifen were associated with increased odds of intentional non-adherence and increased odds of unintentional non-adherence over time, but these did not remain significant in the multivariate analysis. PBC was associated with increased odds of both intentional and unintentional non-adherence but had no significant effects on overall non-adherence over time. This is supported by previous research into medication adherence showing the importance of attitudes and PBC (Kagee & van der Merwe, 2006; Lin et al., 2016). However, in contrast with previous studies (Bane et al., 2006; Lin et al., 2016), subjective

norms were not a strong predictor of non-adherence. Results indicate the usefulness of these variables at understanding tamoxifen adherence and highlight modifiable targets for intervention. The TPB has come under significant criticism in recent years (Sniehotta et al., 2014), with several of the criticisms focussing on the inability of the TPB to predict behaviour in longitudinal analysis. The results from this study provide support for the TPB in understanding non-adherence, but support the criticism that TPB constructs are unable to predict later non-adherence. This makes some theoretical sense, as variables such as PBC are likely to vary over time and are likely to only be relevant to current medication taking behaviour.

As in the cross-sectional study in Chapter 6, differences were seen for the prediction of intentional and unintentional non-adherence. This further supports the conclusions made in Chapter 6 that these behaviours should be targeted separately in interventions. Prediction of total non-adherence provided a similar pattern to unintentional non-adherence, as it was comprised mainly of unintentional non-adherers. Similar to the cross-sectional analysis, demographic and clinical variables, such as ethnicity, job status, chemotherapy and age, were associated with unintentional non-adherence but not intentional non-adherence. More research is needed to identify how to support these women with remembering to take their medication. However, whilst the cross-sectional analyses showed no association between psychosocial variables and unintentional non-adherence, the longitudinal analyses did find some relationships. A higher necessity/concerns differential was associated with a flatter slope for the odds of unintentional non-adherence over time, but this was a relatively small effect compared to the effect on intentional non-adherence. Similarly, more positive attitudes towards tamoxifen and higher PBC were associated with decreased odds of unintentional non-adherence, but the effects on intentional non-adherence were larger. Tamoxifen consequences, distress, side effects and identity showed relationships with intentional but not unintentional non-adherence. Therefore, future research and interventions should make distinctions between intentional and unintentional non-adherence. Similar to the cross-sectional analysis, unintentional non-adherence was reported much more frequently than intentional non-adherence. Therefore, helping women to remember their medication should be a strong focus of any intervention.

Strengths of this study include the large sample size, the longitudinal design, the use of validated models and questionnaires and the robust statistical analysis. However, there were several limitations with the study that should be addressed. First, whilst retention rates were relatively high, significant differences were seen between responders and non-responders. Women who did not respond were more likely to be younger and non-white which suggests that there is a need to attempt to engage these women in the future. Non-responders were

also more likely to be non-adherent at baseline, which creates a bias in the results. There were very few non-white women in the study and yet these women appeared to be more non-adherent. There is a need to conduct future research with a more representative sample in order to explore this relationship further.

To conclude, results show that non-adherence rates rise significantly over a one year follow up period. Unintentional non-adherence was reported more frequently than intentional non-adherence and was associated with a unique set of predictors. Key predictors of non-adherence were ethnicity, medication beliefs, and PBC. The research has identified several potentially modifiable targets which can form the basis of interventions to improve non-adherence in this population. Drawing on the results from Chapters 2-8, the development of a psychoeducational self-management intervention to support BCS taking tamoxifen is described in the following chapter.

9. Development of a psychoeducational intervention to support women taking tamoxifen

9.1. Chapter overview

The current chapter describes the development of a psychoeducational self-management intervention to support breast cancer survivors (BCS) with their tamoxifen treatment. As there is strong evidence to suggest that rates of non-adherence to tamoxifen are high and that non-adherence to tamoxifen is associated with poor clinical outcomes (Hershman et al., 2011), there is a real clinical need to intervene to improve adherence rates. However, to date there have been no published interventions that have attempted to improve adherence to tamoxifen. This chapter first presents an introduction to interventions for improving adherence, before outlining the framework used to develop the current intervention. This framework is then described in detail with an overview of the intervention materials.

9.2. Introduction

Several reviews have concluded that current methods to improve adherence in chronic conditions are complex and not very effective (Haynes, Ackloo, Sahota & McDonald, 2008; McDonald, Garg &Haynes, 2002). These reviews covered a diverse range of interventions, including education, counselling, reminders, family interventions, simplified dosing and Cognitive Behavioural Therapy (CBT). A Cochrane review in 2008 found that while 36 of 83 studies reported improved adherence, only 25 led to improvements in treatment outcome (Haynes et al., 2008). An update of this review reported a lack of convincing evidence among studies with the lowest risk of bias, with only 5 of 17 new studies reporting improvements in adherence and clinical outcomes (Nieuwlaat et al., 2014). Conn and Rupar (2017) conducted a comprehensive review of studies published up to 2015, with 771 papers included. The standardised mean difference effect size between the intervention and control groups was 0.29. The only intervention components associated with better adherence outcomes were habit analysis and pairing adherence to existing habits. The authors concluded that there is much room for improvement in interventions to improve medication adherence rates.

There are several criticisms of the literature on adherence which may explain the lack of effective interventions. Firstly, the majority of previous research has failed to consider both intentional and unintentional non-adherence (Horne et al., 2005). The quantitative analysis in Chapter 6 showed unique correlates for each type of non-adherence, supporting the need to target these behaviours independently. Secondly, previous interventions have been

criticised for not including a theoretical framework or evidence-based theories (Holmes et al., 2014; Horne et al., 2005). Theory based interventions provide a better understanding of what to target in an intervention by specifying a set of potential mechanisms of change. These mechanisms help to evaluate which elements work well within the intervention. They also aid with replicating the intervention results and reproducing the interventions across different contexts or behaviours (Michie, Johnston, Francis, Hardeman & Eccles, 2008). Finally, many previous adherence studies have included any participants regardless of their adherence levels (Nieuwlaat et al., 2014). This creates a ceiling effect which means it is hard to show any effects of the intervention. A review of interventions to improve adherence to anti-cancer drugs found that studies with high rates of baseline adherence did not find differences between intervention and control groups (Mathes, Antoine, Pieper & Eikermann, 2014). Another review found that only 3 of 50 studies screened for non-adherence, making it hard to determine the effectiveness of the interventions in the remaining studies (Jeffery et al., 2014). Moreover, it is not cost-effective to provide interventions to participants who are not in need of assistance with adherence (Hugtenburg, Timmers, Elders, Vervloet, & van Dijk, 2013).

Few interventions have been developed specifically to target Hormone Therapy (HT) non-adherence. Heisig et al. (2015) compared routine clinical information to enhanced information in 137 BCS taking HT in Germany. The enhanced information improved satisfaction with information and knowledge. Higher satisfaction, learning and comprehension directly after the intervention ended were correlated with higher adherence at 3 months follow-up. However, the authors did not report changes over time for adherence and they did not correct for multiple testing. Therefore, it is not possible to know if there were any changes to adherence as a result of the intervention. A similar study was carried out in France to improve adherence to adjuvant HT through a therapeutic educational approach. A three-session educational program was developed based on a series of patient interviews. Medication adherence was not measured, but significant improvements were found in knowledge, and a trend was found for improvements in trust in treatment (Bourmaud et al., 2016).

Several studies have used educational materials (EM) to improve adherence to Aromatase Inhibitors (AIs) specifically. However, none of these studies have shown significant differences in adherence rates between the intervention and control groups (Hadji et al., 2013a; Neven et al., 2014; Yu et al., 2012; Ziller et al., 2013). For example, the PACT study randomised 4844 BCS to EM or standard care (Hadji et al., 2013a). Intervention participants received nine letters and brochures by post as well as monthly medication reminders and low value gifts. There were no significant effects on adherence or persistence. The CARIATIDE

study recruited 2700 women across the world and randomised them to EM or standard care. Intervention participants were sent EM eight times a year, but again, no significant differences were found in adherence across the groups (Neven et al., 2014). Ziller et al. (2013) also compared EM to standard care to improve adherence to AIs in Germany. They randomised participants to one of three conditions; letter group, telephone group or control group. The letter group received information leaflets and reminder letters throughout their treatment. The telephone group received nurse phone calls covering individualised information, feedback to questions and strategies for remembering their medication. Whilst the original analysis across groups showed no significant differences, post-hoc pooled analysis showed that the two intervention groups had significantly higher adherence rates (63% for telephone, 65% for letter) than the control group (48%, p=.039).

There were several limitations with these studies which might contribute to the lack of significant effects. Firstly, the authors provided little information on how they developed the interventions or what the materials were based on. Secondly, validated measures of adherence were not used. Finally, ceiling effects were likely as adherence rates in most of these studies were already very high (up to 95%). In order to elicit a significant change in measured adherence, interventions may need to focus on women who are struggling with adherence, rather than being offered to all women. The lack of a significant effect may also signify the lack of efficacy of EM alone, indicating that they should be combined with other intervention strategies. As yet, no interventions have been carried out to target tamoxifen adherence, and no HT adherence interventions have attempted to move beyond simply providing EM. Therefore, there was a need to develop a more complex intervention which was theoretically based, to try and improve adherence rates in this population.

The current study has overcome the limitations associated with previous studies by using the Common Sense Model of Illness Representations (CSM) and the Theory of Planned Behaviour (TPB) as a framework for intervention development and by basing intervention development on a series of empirical studies. Furthermore, only women who show signs of non-adherence were invited to participate in the study.

9.3. Framework for intervention development

The Medical Research Council (MRC) has provided guidance for the development of complex interventions (Craig et al., 2008). These guidelines recommend that preliminary development work is carried out prior to commencement of a large RCT. This allows researchers to evaluate the feasibility and acceptability of the intervention as well as identifying the key intervention components. The recommendations state that interventions

should be developed systematically based on theory and empirical evidence and should be tested with a series of pilot studies and a definitive evaluation. The current intervention was developed in accordance with the MRC guidance.

As well as following the MRC guidance, the intervention was also developed in line with the Intervention Mapping (IM) framework (Bartholomew et al., 2011; Kok et al., 2016). This framework was developed for health promotion interventions and describes the process for planning and developing interventions in line with theoretical constructs and empirical evidence. A five-stage process based on IM is shown in Figure 9.1. Each stage of IM is informed by the previous stage, but planning is also an iterative process whereby researchers can move fluidly between different stages and revisit earlier stages. Firstly, a needs assessment is carried out. This establishes the extent of the problem and identifies determinants associated with the problem behaviour. The next stage is to identify intervention objectives based on this needs assessment, and to establish which behavioural determinants should be targeted in the intervention. The third stage is to select theory based behaviour change methods and techniques which match the pre-identified determinants, and to translate these into practical applications. The fourth stage of the framework is to integrate these practical applications into an organised programme and to establish the format of the intervention. The final stages relate to the implementation and evaluation of the intervention and are discussed in the following chapter. As mentioned, both the MRC and IM processes are iterative and cyclical and encourage researchers to move between development and evaluation.

Other methods and strategies have also been proposed for intervention development. The IM framework was chosen as it provides a clear overview of how the intervention was developed and why certain strategies were used. Even when studies report basing interventions on theory, very few provide any description on how theory was used to inform the intervention (Michie & Prestwich, 2010). IM was chosen as it overcomes this by clearly specifying the steps involved in intervention development. Furthermore, IM is a flexible process which is not restrained to one single theory, but allows the best theory or evidence based techniques to be bought together.

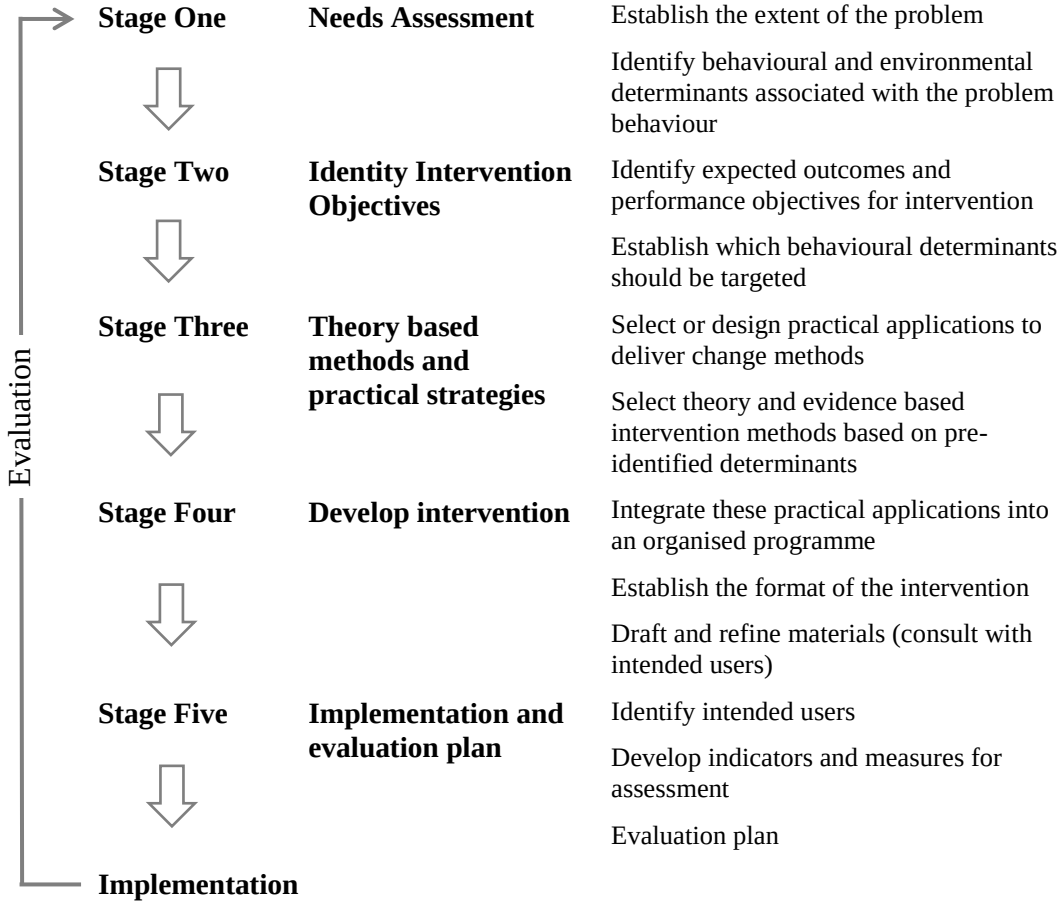

Figure 9.1 Intervention Mapping framework. Adapted from Bartholomew et al. (1998)

9.3.1. Stage one: Needs Assessment

The aim of the needs assessment was to establish the extent of non-adherence in this population and to identify behavioural and environmental determinants associated with non-adherence. The needs assessment was informed by the previous body of research discussed in Chapters 2 to 7. This included a systematic review, qualitative study, cross-sectional study and a longitudinal study. In addition to this, a broader literature review was also carried out. The results of the needs assessment will be discussed in the following sections.

9.3.2. Stage two: Identify Intervention Objectives

The needs assessment highlighted that non-adherence was a problem in this population, and that unintentional non-adherence was reported much more frequently than intentional non-adherence. Furthermore, Chapter 6 showed that there were unique determinants for both intentional and unintentional non-adherence. Therefore, these two behaviours will be targeted separately in the intervention, with a strong focus on helping people to remember to take their medication. Key barriers and facilitators of tamoxifen non-adherence identified by the needs assessment are shown in Table 9.1. Modifying these barriers and facilitators formed the objectives of the intervention. Medication beliefs were a consistent predictor throughout all studies. Chapter 8 showed that the necessity/concerns differential was a significant predictor of later non-adherence after controlling for other covariates. Specific concerns about tamoxifen, such as the risk of endometrial cancer, were identified in the qualitative study (Chapter 4). The cross-sectional and longitudinal studies also identified several illness perceptions which were related to adherence, including lower tamoxifen consequences, higher beliefs around a risk of recurrence, attributing symptoms to tamoxifen and believing that health behaviours can cause a recurrence. Believing that psychological stress caused a recurrence was associated with decreased odds of adherence. However, these illness perceptions were not as strong predictors of non-adherence as the necessity/concerns differential. Chapters 3, 6, and 8 all highlighted that TPB variables were related to adherence. Intentions to take tamoxifen, positive attitudes towards tamoxifen and Perceived Behavioural Control (PBC) were all identified as facilitators of tamoxifen adherence.

Side effects were shown to be a key barrier to adherence across all studies, although results suggest that the impact of side effects on adherence may depend on the patient's illness or treatment beliefs. Chapters 4 and 8 highlighted specific side effects which were bothersome for patients. Chapters 3, 4, 6 and 8 all highlighted social support as a potential facilitator of adherence. Chapter 8 showed that distress may be associated with non-adherence. Knowledge about tamoxifen was also identified as a facilitator of adherence.

Some of these factors overlap or map onto each other and can therefore be targeted together. For example, increasing knowledge should help to increase necessity beliefs and create more positive attitudes towards tamoxifen, which should also increase intentions to take tamoxifen (Bender et al., 2010; Jones, Ellis, Nash, Stanfield, & Broadbent, 2016; O'Carroll et al., 2014). Encouraging more accurate risk of recurrence perceptions may also increase necessity beliefs. Furthermore, women's concerns focused on side effects, and therefore increasing women's confidence in managing side effects may help to reduce their concerns, resulting in

a more favourable cost-benefit analysis. The key aims of the intervention are shown in Figure 9.2.

Table 9.1 Key determinants of non-adherence (and non-persistence) identified by the needs assessment

	Barrier to tamoxifen adherence	Facilitator of tamoxifen adherence
Medication beliefs	Concerns about medication [4] Specific concerns (e.g. risk of endometrial cancer) [4]	Necessity beliefs [3,4,6] Positive differential between necessity and concerns [3,4,6,8]
Illness perceptions	Tamoxifen consequences [6,8] Causal beliefs (psychological attributions) [6]	Risk of recurrence [4,6] Identity [8] Causal beliefs (health behaviours)[6]
Theory of planned behaviour	-	Intentions to take tamoxifen [6] Positive attitude [3, 8] Self-efficacy for taking medication [3] Perceived behavioural control [6,8]
Side effects	Number/intensity of side effect experience [3,4,6,7,8] Specific side effects (e.g. fatigue, vaginal dryness) [4,8]	-
Social support	-	Perceived social support [3,6,8] Importance of support from HCPs, importance of asking for support [4]
Knowledge	Lack of information [3,6]	Having had questions answered/ feeling more informed*
Forgetting	Forgetting [3,6,8]	Tips for taking tamoxifen (good routines) [4]
Distress	Distress [8]	-

[3] Information obtained from Chapter 3, [4]Information obtained from Chapter 4, [6]Information obtained from Chapter 6, [7]Information obtained from Chapter 7, [8] Information obtained from Chapter 8, *Information obtained from additional literature review

9.3.3. Stage three: Theory based methods and practical strategies

The third stage of the IM process was to identify health behaviour change methods and techniques which match the determinants identified in the previous sections. A brief review of potential methods and strategies is presented below. These are then mapped onto the determinants identified in the previous section.

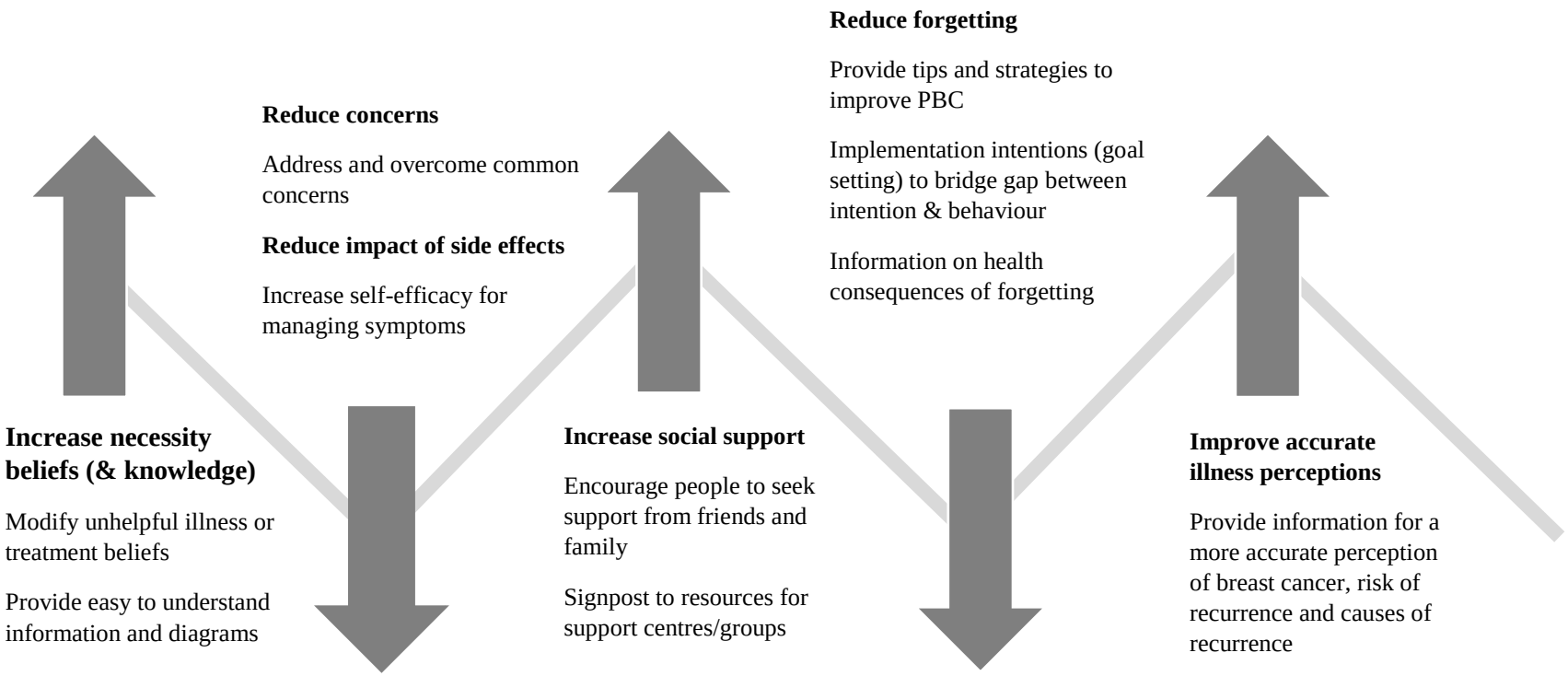

Figure 9.2 Intervention Mapping framework. Adapted from Bartholomew et al. (1998)

9.3.3.1. Modifying illness and treatment beliefs

The CSM posits a self-regulatory process whereby the selection of a coping behaviour, such as adherence, is driven by the patient's illness perceptions. These illness perceptions determine the action plans or coping behaviours used to manage the illness threat. Therefore, there is reason to believe that modifying illness perceptions, to provide a more accurate illness model, may help improve medication adherence by encouraging the use of more appropriate coping strategies. As tamoxifen prevents future recurrence rather than treating current symptoms, patients have no active reinforcement to continue taking their medication. Providing more accurate perceptions of recurrence and illness timeline may help patients to recognise that they need treatment, even when asymptomatic (McAndrew et al., 2008). Modifying additional illness perceptions, such as identity, causal beliefs or consequences may also be beneficial. Several studies have shown that it is possible to modify illness perceptions through intervention (Broadbent, Ellis, Thomas, Gamble & Petrie, 2009; Glattacker, Heyduck & Meffert, 2012; Petrie, Cameron, Ellis, Buick & Weinman, 2002). These interventions focused on providing information to debunk myths, discussing behaviour change methods, symptoms and concerns.

However, few interventions have used these techniques to improve adherence. The few studies conducted in this area have shown some success at improving adherence rates (Elliott, Barber, Clifford, Horne & Hartley, 2008; Seyyesdrasooli, Parvan, Rahmani & Rahimi, 2013). For example, Petrie et al. (2012) used tailored text messages to modify asthma patients' illness and treatment beliefs. Example text messages included 'Your preventer works best if taken every day' and 'Asthma doesn't take a holiday. Even if you don't have symptoms, your asthma is still there.' After 18 weeks of receiving tailored text messages, the intervention group had increased necessity and timeline beliefs. Furthermore, the intervention group showed improved adherence over the follow-up period. A similar study was conducted by O'Carroll et al. (2013) with 62 stroke survivors. Participants were given a simple, brief intervention to modify any unhelpful illness or treatment beliefs and to establish a better medication taking routine. The necessity/concerns differential improved over time, as did adherence, over and above any effect of increased patient contact or mere measurement. Treatment effects were mediated by reductions in forgetting and concerns about medication (O'Carroll, Chambers, Dennis, Sudlow, & Johnston, 2014).

Zwikker et al. (2014b) conducted a group based motivational interviewing intervention in patients with Rheumatoid Arthritis. However, this intervention showed no improvements in adherence, which may be due to ceiling effects, as beliefs and adherence had changed favourably before the intervention took place, during a baseline measurement phase. Bender

et al. (2010) used an interactive voice response intervention based on educational messages and encouraging patients to communicate with Healthcare Professionals (HCPs). The intervention resulted in favourable shifts in necessity/concerns differential, which were correlated with changes in adherence. Karamanido, Weinman and Horne (2008) conducted a psychoeducation intervention aiming to improve understanding of the need for phosphate control in End Stage Renal Disease patients undergoing haemodialysis. This involved patients being given a leaflet and a demonstration of the mode of action. The intervention resulted in positive changes in knowledge, treatment coherence and medication outcome efficacy beliefs in the intervention group in comparison to the control group. However, these improvements were not associated with improvements in perceived need for treatment or for adherence. Similarly, Jones et al. (2016) used a brief animated intervention to improve adherence in acute coronary syndrome. Post intervention, the intervention group had increased treatment control beliefs and decreased medication concerns. At the seven week follow-up, improvements were also seen in timeline beliefs and number of symptoms. These diagrams work by changing intangible information into more concrete recommendations (Jones & Petrie, 2017). However, as with the previous study, these improvements in illness and treatment beliefs were not accompanied by improvements in medication adherence. The authors suggest that improvements may be seen over a longer term follow-up period.

Only a small number of studies have been able to translate changes in illness perceptions to changes in behaviour (Petrie et al., 2012; O'Carroll et al., 2013). There may be methodological issues preventing the remaining studies from seeing improvements in adherence, such as ceiling effects or improper measurement of adherence. Alternatively, the self-regulatory framework may not be operating in the assumed way, meaning that changes to illness perceptions do not result in adjustments to coping behaviours such as adherence. More research with longer term follow-up is needed to determine whether these changes to illness and treatment beliefs will result in changes to adherence behaviour.

9.3.3.2. Changing TPB variables and overcoming forgetting

As with the CSM, previous interventions have also been developed based on the TPB. These interventions target the key TPB constructs; intentions, attitudes, subjective norms and PBC. It is assumed that improving attitudes and PBC will increase intentions to take medication, which should lead to increases in actual medication taking (Ajzen, 1998). For example, a psychoeducational intervention based on the TPB improved adherence and clinical symptoms in children with Attention Deficit Hyperactivity Disorder (Bai, Wang, Yang & Niu, 2015). One of the most popular techniques based on the TPB is implementation intentions, which attempt to bridge the gap between intention and behaviour (Farmer et al.,

2008). Implementation intentions involve pairing a critical cue (i.e. morning coffee) with the goal directed response (i.e. taking medication). They work by establishing a strong habit and removing the cognitive burden for patients to remember their medication. Studies using implementation intentions have been effective at improving adherence rates (Brown et al., 2009; Webb & Sheeran, 2006). In the intervention mentioned previously by O'Carroll et al. (2013), participants were asked to repeat their plan until they could memorise it without looking at it. This increases the automaticity of the response. They found significant improvements in adherence, which were mediated by reductions in forgetting. A psychoeducational program based on the TPB has also improved attitudes and foot care adherence in patients with type II diabetes (Beiranvand, Asadizaker, Fayazi, Yaralizadeh, 2016).

9.3.3.3. Managing side effects

Cancer side-effect management and quality of life (QOL) can be improved with the use of psycho-educational interventions (Badger, Braden & Mishel, 2001; Gaston-Johansson et al, 2013; Golant, Altman & Martin, 2003). These interventions include strategies such as providing clinical information about side effects, sharing experiences to empower patients, cognitive reframing, enhancing problem solving and coping skills, and relaxation. CBT techniques can also help with successful symptom management. CBT models have been developed to help people understand how their symptoms might be affected by their thoughts, feelings and behaviours, and to identify precipitating and perpetuating factors associated with the symptom. Guided and self-management CBT interventions have been shown to reduce fatigue in illnesses such as breast cancer and Multiple Sclerosis (Gielissen, Verhagen & Bliejenberg, 2007; van Kessel et al., 2008; Moss-Morris et al., 2012). These treatments involve targeting cognitive and behavioural variables which are associated with fatigue, such as all-or-nothing responses or negative beliefs about fatigue (Skerret & Moss-Morris, 2006). CBT interventions have also been successful in reducing the impact of hot flushes and night sweats (HFNS) in BCS (Mann et al., 2012). This is based on a cognitive model of HFNS which explains how the perception, attribution and appraisal of menopausal symptoms are influenced by cognitive factors, beliefs and mood (Hunter & Mann, 2010). For example, negative thoughts such as embarrassment, disgust and worry are linked to more problematic hot flushes (Rendall, Simonds & Hunter, 2008). Group CBT sessions significantly reduced HFNS problem rating at 9 and 26 weeks (Mann et al, 2012). Women in the CBT group also reported better social/physical functioning and improved general health.

9.3.3.4. Improving knowledge

Previous educational interventions have been shown to improve medication adherence in a range of conditions (Clerisme-Beaty et al. 2011; Munoz, Dorado, Guerrero & Martinez, 2014; Newman-Casey et al., 2013; Yu, Chair, Chan & Choi, 2015; Zullig, McCant, Melnyk & Danus, 2014). Studies have also shown that educational interventions can result in clinical improvements (Kuntz et al., 2014). However, other studies have found that educational materials are not effective at improving medication adherence (Alvaro et al., 2015; Sabate, 2003). Costa et al. (2015) concluded that whilst educational interventions can improve knowledge, they often do not influence adherence levels, suggesting that it may be more effective to combine patient education with behavioural interventions. This is supported by the studies described previously showing a lack of an effect of educational materials on AI adherence (Hadji et al., 2013a; Yu et al., 2012; Ziller et al., 2013). This suggests that education or knowledge may be beneficial for improving adherence but they are not sufficient alone.

9.3.3.5. Overview of methods and strategies

The key determinants of tamoxifen non-adherence are shown in Table 9.1. Based on the techniques described above, Table 9.2 maps specific methods and techniques on to these key determinants. Several of these strategies overlap, such as providing information on how tamoxifen works, which should increase knowledge as well as necessity beliefs and potentially increasing intentions to take tamoxifen and attitudes towards tamoxifen. As shown in Table 9.2., these methods and strategies are targeted in different sections across the intervention. They will be discussed in turn in the relevant sections below.

9.3.4. Stage four: Develop intervention

9.3.4.1. Format of intervention

A key step in this stage of intervention development was to establish the format of the intervention. In this case, a self-management intervention was chosen as it was felt this would have the widest reach. Many tips for improving non-adherence to tamoxifen focus on the patient/provider relationship and the healthcare setting (McCue, Lorh & Pick, 2014; Partridge et al., 2007), but this is less relevant in the UK where patients are receiving less contact with their physician. The NHS is currently implementing Open Access Follow Up, which means that regular follow-up clinics will be replaced with annual mammograms and appointments with Clinical Nurse Specialists (CNS) where needed. BCS are being encouraged to manage their own care and therefore a self-management intervention was an

appropriate choice within this context. As the intervention requires very little input from researchers or clinicians, it also has the potential to be widely rolled out at a very low cost, which improves clinical utility (Jones et al., 2016). The MRC guidance recommends that researchers think about implementation at early stages of intervention development, which is in line with Normalisation Process Theory (NPT; Murray et al., 2010), which suggests that failing to consider implementation at the early stages may result in an intervention which is effective but not able to be implemented. NPT outlines a process for creating an intervention which can become embedded into normal practice, such as involving stakeholders at early stages of the research, thinking about who will deliver the intervention, what the costs will be and what the context or setting for the intervention will be. A full application of NPT was not feasible during the development of this intervention but it was felt that a self-management intervention, if successful, had more potential to be implemented as it does not require many resources.

Similar self-management interventions have been well received by patients and have improved a range of clinical and psychosocial outcomes (Coffey et al., 2016; Goldberg, Hinchley, Feder & Schulman-Green, 2016; Lee et al., 2014). For example, Taking CHARGE is a self-management program for BCS which provides women with the skills to self-manage concerns and provides information on survivorship topics. The program was well received with women reporting that it was timely, relevant and had high utility. As well as improving QOL, self-management interventions have shown promise in improving adherence rates. Anglada-Martinez et al. (2016) found that while a medication self-management app did not approve adherence rates as measured by prescription refill rates, there were improvements in self-reported adherence rates. This intervention included good adherers at baseline which may explain the lack of an effect on objective measures of adherence. The World Health Organisation (WHO) report on medication adherence suggested that interventions aiming to enhance self-management or self-regulation capabilities may be the most effective interventions (Sabate, 2003).

Table 9.2 Key behaviour change strategies used in intervention

Key determinants	General method for addressing determinant	Specific strategies/techniques	Intervention Section
Medication beliefs	Increase necessity beliefs	*Provide evidence and information on why tamoxifen is necessary, how it works and what happens if doses are missed, visual information (diagrams) to demonstrate the mode of action, quotes/ videos for social comparison.*	1,2
	Address concerns	*Provide information to address common concerns (e.g. risk of endometrial cancer), activity to list concerns and come up with response for concerns, challenge any misperceptions about medication.*	1,2,3
Illness perceptions	Challenge unhelpful beliefs about illness	*Provide information to modify inaccurate perceptions (e.g. causal beliefs, risk of recurrence, identity) and challenge unhelpful beliefs.*	1,2,3
	Reduce tamoxifen consequences	*Provide tips to increase self-efficacy for symptom management, goal setting exercise, videos and quotes for social comparison.*	3
Theory of planned behaviour constructs	Increase intentions, develop more positive attitudes	*Address concerns associated with tamoxifen, provide information and evidence on tamoxifen to encourage more positive attitudes, activity to address concerns, information on consequences of forgetting/missed doses.*	1,2,3
	Bridge gap between intentions and behaviour	*Implementation intentions, goal setting/action planning, evaluation of goal setting.*	2
	Improve perceived behavioural control	*Provide tips for taking tamoxifen, social comparison, goal setting/action planning.*	2
Side effects	Develop coping skills and enhance self-efficacy	*Symptom monitoring, provision of practical tips and coping strategies for common side effects, quotes and videos for social comparison, enhance confidence for dealing with symptoms, psychoeducation on why common side effects occur.*	3

Key determinants	General method for addressing determinant	Specific strategies/techniques	Intervention Section
Side effects	Develop coping skills and enhance self-efficacy	*Symptom monitoring, provision of practical tips and coping strategies for common side effects, quotes and videos for social comparison, enhance confidence for dealing with symptoms, psychoeducation on why common side effects occur.*	3
	Set goals for managing symptoms	*Formulate SMART goals, implement goals, evaluate goal setting.*	3
	Use CBT strategies to help reduce impact of HFNS	*Psychoeducation on the physiology of HFNS, identify potential triggers, challenge negative thoughts about HFNS, develop more helpful responses, paced/diaphragmatic breathing.*	3
Social support	Increase perceived social support, encourage women to seek support	*Provide information on the importance of asking for help, quotes and videos for social comparison. Provide resources for seeking social support elsewhere and for seeking professional help.*	4
Knowledge	Information provision	*Psychoeducation, visual information, signposting to further information, evaluation of knowledge.*	1,2,3
Forgetting	Strategies to help remember to take tamoxifen, increase motivation to remember	*Social comparison, practical tips, implementation intentions, information on consequences of non-adherence.*	2

9.4. Developing and piloting the intervention content

Before the intervention was written, interviews were carried out with three patient representatives. In these interviews, women discussed ideas for the overall content of the intervention and the format of the materials. The intervention was developed in an iterative process following the key determinants and strategies identified in stages two and three of the IM framework. These strategies were grouped into sections which were reviewed by the research team. The material was then written up, with input from the research team. The MRC guidance recommends that patients or 'users' are involved in all stages of the development, process and analysis of a complex intervention. Once finalised within the research team, the written sections were emailed to nine patient representatives. Women read

each section and sent feedback by email or telephone. The first chapter was also reviewed by two clinical nurse specialists. The overall feedback was very positive (Table 9.3), but some small changes were made based on patient feedback. Constructive suggestions included reducing some repetitive information, adding additional infographics and providing additional clinical information. Negative feedback tended to be focussed more around pragmatic issues, such as the use of the colour pink or the ordering of some information. One woman was not happy with the quotes presented from other BCS, but the general feedback for these was positive. The intervention booklet is included in Appendix I, along with the accompanying Activity Booklet.

The intervention booklet includes quotes from other BCS taken from the qualitative study presented in Chapter 4. As well as these quotes, several videos were made where BCS discussed their experiences and provided tips on how to manage tamoxifen. These types of videos have been found to be one of the most powerful tools in self-management interventions (Clarkesmith, Pattison, Borg & Lane, 2016). The aim was to normalise the experiences that women are going through and to let them know that they are not alone. Coffey et al. (2016) found that hearing other people's experiences helps patients to validate their own experiences. Furthermore, it was hoped that these videos would help to legitimise the project and show it has been developed with help from other BCS. Initial patient feedback suggested that women may be sceptical of any support materials which had been created by people who had not gone through cancer or tamoxifen treatment.

Table 9.3 Feedback on the intervention materials from patient representatives

Quotes from PPI representatives on the intervention materials
"Very excited about this booklet as it is desperately needed"
"I think it's great!! It's easy to read, very informative, more so than when I was originally diagnosed. The exercises are a great idea"
"This all looks great to me, really informative and I can't think of anything that you haven't covered. I wish I had something like this to read when I started Tamoxifen!"
"The diagrams are brilliant as they really help explain everything"
"The information given is very detailed and useful. I especially like (and can identify with) the comments given by ladies taking Tamoxifen."
"Wish I'd had this booklet from the beginning!"
"All I can say is wow. I have read through all of it and have made mental notes to myself on how I will cope for the next 5 years. I can't see anything negative to report back on"

Note. PPI Patient Public Involvement

The booklet is separated into four sections (Table 9.4). All women complete section one. At the end of section one, women perform a needs assessment where they identify which sections will be most beneficial for them. This involves women answering a series of questions to determine which issues they are struggling with. They then complete one or all of the following sections. The sections were developed following the determinants and strategies identified in Table 9.1 and 9.2.

Table 9.4 Intervention sections

Intervention sections	
Section one	What is tamoxifen
Section two	How to take tamoxifen
Section three	Managing common side effects
Section four	Finding and utilising support

9.5. Intervention content

9.5.1. Section 1: What is tamoxifen?

The first section of the booklet provides information on what tamoxifen is and how it works. This was included at the start of the intervention as it was felt that it would be relevant for all participants, and it was an easy section to ease them into the booklet. Information is provided under a series of subheadings, covering breast cancer, risk of recurrence, the role of oestrogen, how tamoxifen works, how effective it is and why it is important to take it every day. Each of these subsections includes easy to understand information, tested using the Flesch Kincaid reading comprehension score set to age 12. Each page includes a glossary of key terms to support participants' understanding of key concepts. In addition to this, diagrams are used to supplement the written material. For example, one diagram shows how oestrogen receptors work and illustrates the mechanism of action for tamoxifen (Figure 9.3). An additional diagram also demonstrates what would happen if doses of tamoxifen were missed. A figure was created to illustrate the risk of recurrence per 100 women with and without tamoxifen. At the end of the section, women are signposted to resources for further information or support.

The rationale for this section was based on previous literature showing that many women reported a need for more information about HT. For example, focus groups have shown that BCS wished they had access to a knowledge source showing how their medication works and why they have been prescribed it (Van Londen et al., 2014b). These wishes were echoed by participants in the qualitative study presented in Chapter 4. Studies across Europe show that only 67% of women understood why they had been prescribed HT, only 57% reported

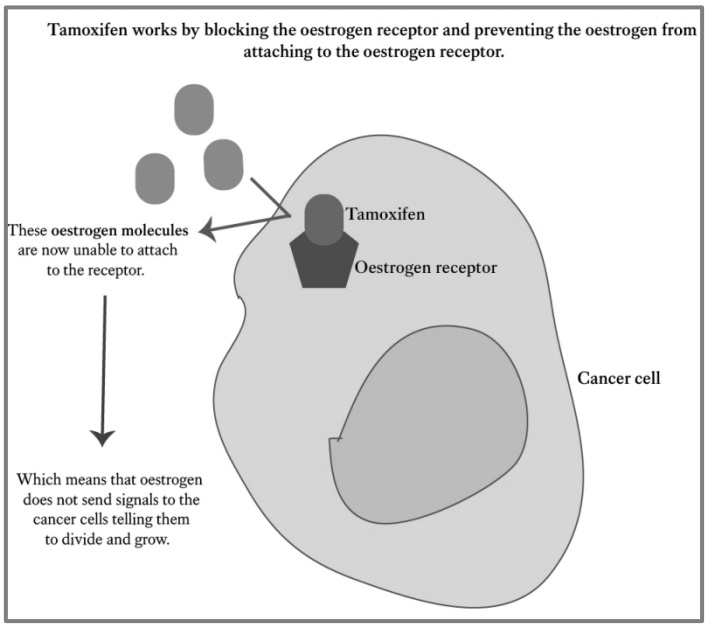

Figure 9.3 Diagram showing mechanism of action for tamoxifen

receiving information about side effects, 26% reported receiving information about risk of recurrence and only 13% felt their questions were answered (Quinn et al., 2016; Wengstrom, Aapro, Leto di Priolo, Cannon & Georgiou, 2007; Wuensch et al., 2015).

There is a need to overcome this knowledge deficit in order to support BCS with making an informed choice about treatment. Furthermore, this information deficit has been linked to adherence rates. Many researchers and clinicians have proposed that providing clear information on how tamoxifen works should improve adherence rates by increasing positive beliefs about tamoxifen (Arriola et al., 2014; Burstein et al., 2014; Fink et al., 2004; Wengstrom, 2008). This has been supported by a range of other studies. Longitudinal and cross-sectional studies have shown that women who have their questions answered and who feel more informed about their HT have better adherence and persistence (Cluze et al., 2012; Sheppard et al., 2014; Wouters et al., 2014; Wuensch et al., 2015). Grunfeld et al. (2005) found that 50% of non-adherers reported that no benefit could be gained from taking tamoxifen, compared to just 16% of adherers. Providing information on the clinical benefits

of tamoxifen is particularly important in a medication like tamoxifen where the benefits are hidden, and where no reduction in symptoms can be attributed to medication taking (Meyer et al., 1985). This means there is no overt positive reinforcement for the patient to continue taking the medication. As discussed earlier in the chapter, previous educational interventions have been effective at improving adherence rates (Clerisme-Beaty et al., 2011; Newman-Casey et al., 2013).

Some of the information presented in Section 1 focuses on what would happen if doses were missed. This was included because the qualitative study in Chapter 4 showed that women talked about skipping or halving doses or taking long treatment breaks but still wanting to appreciate the full clinical benefits of treatment. This was also found in Harrow et al.'s (2014) qualitative study, in which women often missed tablets without realising the full potential consequences of this action. In an online survey, 89% of BCS reported that knowing adherence would improve clinical outcomes was an important factor for improving adherence levels (Kirk & Hudis, 2008). The rationale for including diagrams in this section was to cater for women who preferred a more visual style of learning. Previous health interventions have been shown to be more effective when they contain visual elements as well as written information (Joplin, van der Zwan, Joshua & Wong, 2015). Furthermore, providing visual imagery around medication taking has been shown to improve adherence in several studies (El Miedany, Gaafary & Palner, 2012; Perera, Thomas, Moore, Faasse & Petrie, 2014).

Fear of recurrence or perceptions of the risk of recurrence have been associated with adherence (Table 9.1). Section one covers information on risk of recurrence, aiming not to increase people's fear and to scare them into taking tamoxifen, but to provide clear information on what the risk means and what the overall risks are, to ensure patients are fully informed. Participants are asked to assess their confidence in their knowledge about different aspects of tamoxifen pre- and post- reading Section one. After finishing Section one, women review which sections of the booklet they feel will be most helpful and to move on to the corresponding section.

9.5.2. Section 2: How to take tamoxifen

Section two focuses on how to take tamoxifen and addresses both forgetting to take tamoxifen and deliberately skipping doses. The aim throughout this chapter is to educate patients on the importance of taking tamoxifen as prescribed, whilst normalising forgetting and understanding that for some women, non-adherence or non-persistence may be the best solution based on their risk level and their QOL. The aim was to reassure women and encourage them to make the decision that was right for them, whilst stressing the importance

of discussing any changes to their medication with their Breast Team. Participants complete a short activity to decide which non-adherent behaviours are relevant for them, before reading the corresponding sections.

As forgetting was reported much more frequently than deliberately skipping doses in the quantitative analysis, this behaviour is addressed first and is allocated more time. As discussed above, efforts were made to ensure that the language remained non-judgemental. The information and diagrams in section one relating to what happens when doses are missed is reiterated here, as understanding what would happen when doses are missed appears to be an important part of improving adherence (Chapter 4; Cheung, Lai, Ruan, Chang & Setoguchi, 2015; Harrow et al., 2014; Kirk & Hudis, 2008; Wells et al., 2016). Participants are given tips from other women on how to remember to take tamoxifen, what to do when going on holiday and how to improve planning. These tips were largely taken from the qualitative study presented in Chapter 4. After reading these tips and learning about the importance of taking tamoxifen as prescribed, participants are referred to an implementation intentions activity. In this activity, women pair the behaviour of taking tamoxifen to a key activity in their day, such as a morning cup of coffee. This increases the automaticity in which the behaviour is performed and removes the burden of having to remember. Participants write their plan down in the template provided, visualise it and repeat it until they know it from memory. Example plans are provided to help give participants inspiration. Several similar interventions have shown success of these activities at reducing rates of forgetting (Brown et al., 2009; O'Carroll et al., 2013; Webb & Sheeran, 2006).

The rationale for this activity was based on the evidence from the needs assessment that self-efficacy for medication taking, PBC and intentions were predictors of adherence, and evidence from the qualitative study showing that many adherent women had good routines in place (Table 9.1). Furthermore, in a large review of interventions to improve adherence, significantly larger effect sizes were found for interventions which linked medication taking with existing habits or which incorporated prompts (Conn, Ruppar, Enriquez & Cooper, 2016).

A subsection in this section is dedicated to deliberately skipping doses. Again, efforts were made to ensure that language was non-judgemental. However, in order to ensure that women were making fully informed decisions about these behaviours, information was provided on the clinical implications of missing doses. Women are also encouraged to discuss their concerns with their HCPs in order to find the best solution for them. Five key concerns are addressed; I can't see tamoxifen having an effect; I have a lot of side effects; I don't want to

get another type of cancer; tamoxifen is a reminder that I am unwell; and I prefer to use natural products and medicines. These concerns were drawn from previous literature and the qualitative study conducted in Chapter 4. After reading responses to these concerns, women are asked to complete an activity where they can list their own concerns and create a response to overcome the concerns. Examples are provided to help women understand this activity. For example, a concern around getting another type of cancer is overcome by stating that the chance of getting endometrial cancer is tiny, and whilst tamoxifen does increase this, it is still only a tiny risk compared to the benefits of taking tamoxifen.

9.5.3. Section 3: Side effects of tamoxifen

The third section is on how to manage common side effects. Women are given information on what side effects may be associated with tamoxifen and general tips for symptom management. They are introduced to the link between thoughts, feelings and behaviours. Participants complete a symptom monitoring diary before reading the sections for the side effects which are troubling them. After reading the corresponding tips, participants are referred to information on tips for SMART goal setting, along with example goals for each side effect. Women create their own goals for symptom management and spend two weeks trying to implement this goal, before reviewing its effectiveness. The side effects were chosen based on the information in Chapter 4 and Chapter 6 and included (1) HFNS, (2) vaginal dryness/itchiness/discharge, (3) tiredness/fatigue, (4) changes in mood, (5) weight loss, (6) leg cramps/joint pain. Each of these subsections included a description of the symptom, an explanation of why people might experience the symptom and tips for managing the symptom.

The section on HFNS was informed by the successful CBT treatment for HFNS (Mann et al., 2012). Participants were also provided with a video of Professor Myra Hunter describing the treatment. A paced breathing exercise is provided to help women remain calm through the hot flush. Other tips are also provided on how to keep cool and how to avoid HFNS triggers. The sections on tiredness, fatigue and insomnia also utilise CBT techniques by reiterating the link between thoughts, feeling and behaviours and providing fatigue management techniques such as balancing rest and activity, keeping a fatigue diary and practising good sleep hygiene. The remaining sections provide a range of different tips for managing the symptoms, as well as quotes from BCS and resources for more information or support.

This section was included because side effects are consistently identified as a barrier to adherence in qualitative and quantitative studies (Grunfeld et al., 2005; Moon et al., 2017b; Wells et al., 2016), with many researchers suggesting that reducing side effects should

improve adherence rates (Chirgwin et al., 2016; Doggrell, 2011; Kirk & Hudis, 2008). Evidence suggests that patients weigh their side effects up against their necessity beliefs when making decisions about taking tamoxifen. Reducing the impact of side effects may cause the cost-benefit analysis to become more favourable. Studies suggest that women often feel unprepared for the side effects and that they are given little support in dealing with them (Moon et al., 2017b; van Londen et al., 2014b; Wuensch et al., 2015). Researchers have suggested that knowing what side effects to expect may help patients to deal with them, potentially improving adherence (Fallowfield, 2008; Partridge et al., 2007; Wood, 2012). Qualitative studies have shown that women often do not feel recognised and validated by their HCPs, which makes the burden of HT heavier (Moon et al., 2017b; Verbrugghe et al., 2015). One aim of this section was to help patients to feel recognised and validated in their experiences. This was also achieved by the inclusion of quotes and videos of other BCS.

The aim of the section was not to remove the side effects, but to improve women's confidence in dealing with them and to reduce their impact on QOL. In patients with haematological disease, non-adherence was found to be associated with the difficulty of handling side effects, rather than the presence or frequency of side effects (Richardson, Marks & Levine, 1988). Furthermore, in BCS, greater self-efficacy for coping with symptoms was associated with greater functional, emotional and social wellbeing after controlling for physical symptoms (Shelby et al., 2014). Self-efficacy also mediated the relationship between wellbeing and physical symptoms. If a woman had high self-efficacy for coping with symptoms, then physical symptoms had no impact on wellbeing. In addition to this, the quantitative analysis in Chapter 6 showed that tamoxifen consequences was related to non-adherence. Therefore, this section aims to help women feel more confident in coping with these symptoms, and reduce the consequences of taking tamoxifen on people's daily lives.

9.5.4. Section 4: Support

The final section focuses on social support. This is the shortest section and was included as evidence from the needs assessment suggested that increased social support may be associated with higher rates of adherence and persistence (Table 9.1). This section discusses why women may still need support at this stage in their treatment, and why it is important to ask for help. This was included as women in the qualitative study complained that their friends and family underestimated the impact of tamoxifen and expected them to be 'back to normal'. Women are given information on the importance of telling their friends and family if they are struggling with tamoxifen and are encouraged not to worry about feeling a burden. As well as encouraging women to talk to their significant others, alternative sources

of social support are also discussed. A list of potential online groups is provided, along with quotes from other women showing how helpful they found these groups. The benefits of face-to-face groups are then discussed and women are referred to websites to find local groups. Finally, a list of helplines and support centres is presented. The final section encourages women to discuss their concerns with their HCPs, especially with regards to discontinuing tamoxifen treatment. Tips for communicating with HCPs are provided, both for overall discussions and for more sensitive topics.

9.6. Summary

This chapter described the development of a psychoeducational self-management intervention to support BCS taking tamoxifen. The intervention was developed following the IM framework and was informed by empirical research and theories of health behaviour. The initial feasibility and acceptability testing of the intervention is described in the following chapter.

10. Feasibility and acceptability of a psychoeducational intervention for breast cancer survivors prescribed tamoxifen

10.1. Chapter overview

This chapter describes the initial feasibility and acceptability testing of a self-management psycho-educational intervention to support Breast Cancer Survivors (BCS) taking tamoxifen. The intervention provides information and activities with the aim of increasing necessity beliefs and knowledge, decreasing concerns about tamoxifen, helping women to manage their symptoms, modifying unhelpful illness perceptions, and increasing perceived behavioural control (PBC). The intervention was informed by the research described Chapters 3, 4, 6, 7 and 8. The development of the intervention is described in Chapter 9.

The Medical Research Council guidance on developing complex interventions recommends that feasibility testing is carried out prior to a large randomised controlled trial (RCT) (Craig et al., 2008). These feasibility studies are useful as they can determine whether an intervention is appropriate for further testing, they can identify any methodological challenges, and they are helpful for planning and justifying later RCTs (Anderson & Prentice, 1999; Bowen et al., 2009; Feeley et al., 2009). These studies can also assess the acceptability of the intervention. Whilst feasibility assesses the ability to provide the intervention and conduct the study, acceptability measures the suitability or favourability of the intervention from the service user's perspective (Feeley et al., 2009). Questions to be assessed in feasibility studies include whether the recruitment strategy is feasible, if there is any interest in the study, if the target population is large enough, if the study procedures are feasible, if the timeframe is sufficient and whether any additional resources are needed. Establishing these issues in pilot or feasibility studies reduces the likelihood of any problems at the RCT stage (Fain, 2010). Feasibility studies may include randomisation even if they are not powered to detect differences between groups. This helps to test the feasibility and acceptability of the randomisation procedures. However, due to time constraints, it was not possible to randomise participants in this study. Non-randomised feasibility studies, however, still enable the intervention and other study processes to be evaluated prior to a future larger trial and they therefore still add value. A recent review found that around a third of pilot or feasibility studies were non-randomised (Eldridge et al., 2016).

10.1.1. Study aims

The primary outcomes are of the study are:

1. To assess the feasibility of delivering the intervention to women by measuring:

a) The percentage of eligible women within the recruitment centres
b) The percentage of eligible women agreeing to participate (the uptake rate)
c) The percentage of women completing the intervention (the retention rate)
d) The percentage of women who switch medications during the intervention period.

The secondary outcomes are to:

1. Calculate effect size of any changes in adherence rates
2. Calculate effect size of any changes in illness and/or treatment perceptions which are related to adherence
3. Calculate effect size of any changes in quality of life (QOL), distress, confidence in dealing with symptoms, and satisfaction with information about medicines.

10.2. Methods

10.2.1. Ethical approval

Full NHS REC and HRA approval was granted by London South East Research Ethics Committee (REC Ref: 16/LO/1205).

10.2.2. Design

An exploratory pre-post design was used with all participants being allocated to the intervention condition. The intervention duration was around four to six weeks.

10.2.3. Participants

10.2.3.1. Inclusion and exclusion criteria

The inclusion criteria for the study were:

(i) Diagnosis of primary breast cancer
(ii) Prescribed adjuvant tamoxifen
(iii) Over the age of 18
(iv) Able to consent for themselves
(v) Ability to read and understand English
(vi) Suboptimal levels of adherence, as evidenced by scoring < 25 on the Medication Adherence Rating Scale (MARS).

The exclusion criteria for the study were:

(i) Diagnosis of secondary or metastatic breast cancer

(ii) Prescribed course of tamoxifen has ended, or is due to end during the study period

(iii) Received a diagnosis of depression in the past year

10.2.3.2. Recruitment

Recruitment took place over 6 months (November 2016-April 2017). Participants were recruited through breast clinics, online advertisements and through a previous database of participants.

Recruitment through breast clinics

Patients were recruited through breast clinics at four NHS trusts. Clinic staff identified potential participants. If patients were interested in the research they were given an information sheet and had the opportunity to ask any questions about the research. They then completed a Screening Questionnaire to assess their eligibility, including the MARS. Informed consent was taken from eligible patients who were interested in taking part. Recruitment at three London NHS trusts was carried out by local clinic staff, and recruitment at the final trust was carried out by the research team.

Online recruitment

Advertisements were placed on Facebook support groups, with permission by group admins. The advertisements provided some brief information about the study and asked interested patients to contact the researcher for more information. Patients were then sent the Information Sheet, Consent Form and Screening Questionnaire and were asked to return these to the researcher by email or post.

Recruitment through previous database

As part of the previous cross-sectional study (Chapter 6), participants were asked if they consented to being contacted about a future intervention study. Participants who consented to this were screened based on the information they provided as part of the previous study. Participants who were potentially eligible were sent an invitation letter or email, along with the Information Sheet, Consent Form and Screening Questionnaire. Patients were asked to complete the forms and return them to the researcher if they were interested in taking part. They had the opportunity to ask questions before providing consent. The forms could be returned by email or post, depending on the participant's preference.

10.2.4. Procedure

Once informed consent had been taken, participants were given the baseline questionnaire to complete. They could do this on paper and return it to the researcher using a stamped addressed envelope, or complete the questionnaire online. The online questionnaire was hosted on Bristol Online Survey and took around 15 minutes to complete. If the baseline questionnaire was not completed within a week, a reminder email or letter was sent. After completing the baseline questionnaire, women were sent the intervention booklets (Appendix I). Once the intervention materials were complete, participants were asked to answer the follow up questionnaire, which they could either do online or as a paper copy. Participants were then invited to take part in an interview to discuss their experiences of the intervention. These interviews took place over the phone and lasted around 20 minutes. They were based on a semi-structured interview schedule. Participants were encouraged to guide the interview and to bring up topics which they felt were relevant. They were asked how they found the intervention, what was particularly helpful and what could be improved.

10.2.5. Outcome measurements

Primary outcomes

The primary outcome was to assess the feasibility and acceptability of the intervention. The feasibility was assessed by measuring:

a. The percentage of eligible women within the recruitment centres.
b. The percentage of eligible women agreeing to participate (i.e. the uptake rate).
c. The percentage of women remaining until the close of the study (retention rate).
d. The percentage of women who switch medications during the intervention period.

The acceptability was measured using semi-structured interviews with women who took part in the intervention, and by the percentage of women who completed the intervention. Unfortunately, it was not possible to analyse the interviews within the time frame of the PhD and they will therefore be presented at a later date.

Secondary outcomes

Medication Adherence Report Scale (MARS)

The MARS (Horne et al., 2001) includes five statements about taking medication, which are each scored on a five-point scale from never to always. The scale attempts to avoid any issues regarding social desirability by asking questions in a non-threatening and non-judgemental way. It includes four questions on intentional non-adherence and one on unintentional non-adherence. The scale has demonstrated good internal reliability and test-

retest reliability (reliability coefficient: 0.83; Horne et al., 2001). It has been used multiple times in breast cancer patients (Boonstra et al., 2013; Kim et al., 2014). As well as completing the MARS, patients were asked a single question to determine if they had discontinued tamoxifen treatment, and if so, why.

Beliefs about Medicines Questionnaire (BMQ)

The BMQ-Specific measures beliefs surrounding the necessity of taking medications and concerns about adverse effects (Horne et al., 1999). Each item is rated on a 5 point Likert type scale. A higher score on each subscale indicates stronger necessity or concern beliefs. The scale has been used many times in breast cancer patients with Cronbach's alpha values of 0.79–0.86 and 0.72–0.84 for the necessity and concerns scales, respectively (Bender et al., 2014; Corter, Findlay, Broom, Porter, & Petrie, 2013; Jacob Arriola et al., 2014). The word 'medication' was replaced with 'tamoxifen' on all items.

Revised Illness Perceptions Questionnaire for Breast Cancer Survivors (IPQ-BCS)

The IPQ-BCS was used to measure illness perceptions (Moon et al., 2017c). This is a modified version of the Revised Illness Perceptions Questionnaire (IPQ-R). The development and validation of this scale is described in Chapter 5. The IPQ-BCS shows good psychometric properties. It contains ten subscales; identity, tamoxifen consequences, breast cancer consequences, cure, risk of recurrence, treatment control, personal control, coherence, emotional representations and causal beliefs. The identity scale includes a list of symptoms where participants are asked to indicate if they have experienced a symptom and if they attribute it to their breast cancer or tamoxifen treatment. The causal beliefs scale includes two subscales, psychological stress and health behaviours. Participants tick on a five-point scale to indicate the extent to which they agree or disagree that each factor causes a recurrence. The remaining scales each include four items scored on a 5-point Likert-type scale, with participants indicating the extent to which they agree or disagree with each item.

Hospital Anxiety and Depression Scale (HADS)

The HADS is a 14-item measure with depression and anxiety subscales (Zigmond & Snaith, 1983). The overall Global Distress scale was used in this study, as a recent study has suggested the scale does not differentiate well between anxiety and depression (Norton et al., 2013). Each item is scored on a scale of 0 – 3, with higher scores reflecting higher levels of depression and anxiety. Internal consistency values in patients with breast cancer were α=0.81 – 0.86 for depression and α=0.83 – 0.85 for anxiety (Matthews et al., 2014; Stanton et al., 2014).

Quality of life

The FACT-ES is a QOL scale for patients with breast cancer who are on endocrine therapy. The FACT-ES has demonstrated good test-retest reliability (Fallowfield et al., 1999). Patients provide an answer on a five-point scale from 'not at all' to 'very much' to indicate how much they have experienced each concern. It contains subscales on physical wellbeing, functional wellbeing, social/family wellbeing and emotional wellbeing. An additional concerns subscale lists potential side effects of endocrine treatment that women may have experienced.

Confidence in dealing with symptoms

To identify whether women feel confident in their ability to manage their symptoms, a modified version of a standard self-efficacy scale was used. The scale asks women to rate their confidence in their ability to cope with a series of symptoms on a 10-point scale ranging from 10 (not confident) to 100 (very confident). This modified self-efficacy scale has been used previously in this population and has shown good reliability (Shelby et al., 2014).

Satisfaction with Information about Medicines Scale

The Satisfaction with Information about Medicines Scale (SIMS) was used to determine how informed people feel about 17 different aspects of their treatment. Answers range from "Too much" to "Too little", with additional options for "None needed" and "None received". The SIMS shows satisfactory internal consistency and test-retest reliability (Horne et al., 2001). It has been used previously in a sample of women with breast cancer and has shown good reliability (0.90; Heisig et al., 2015).

10.2.6. Intervention

The intervention involved participants completing the materials described in Chapter 9 (Appendix I). Participants were sent the Intervention booklet and the accompanying Activity booklet. An initial phone call was then carried out with participants, where they were given an overview of the materials by the researcher, and asked to identify which areas may be particularly beneficial for them. This phone call lasted around ten minutes. Participants then worked through the four sections of the booklet and the associated activities for four to six weeks. The researcher telephoned participants two to three weeks into the intervention to give additional support with the activities and to discuss goal-setting. This also served as a reminder for participants to engage with the materials. Participants were then left to complete the rest of the materials, with the option of contacting the researcher to discuss any questions or concerns.

10.2.7. Statistical analysis

Sample size calculation

Little guidance is provided on the required sample size for feasibility studies. The National Institute for Health Research (NIHR) recommends that the sample size needs to be large enough to estimate the proportion of eligible people who are willing to participate, of participants who drop out of the trial or of participants who comply with their intervention (NIHR, 2015). A review of previous feasibility studies found that the average study had 36 participants per arm (Arain, Campbell, Cooper, & Lancaster, 2010). This is consistent with recommendations given by Lancaster, Dodd, and Williamson (2004) who suggest an overall sample size of 30. Other recommendations range from 24 (Julious, 2005) to at least 50 (Sim & Lewis, 2012). Based on these recommendations, the recruitment aim for this study was 40 participants to account for an expected attrition rate of 20%.

Statistical analysis

Statistical analysis was carried out using SPSS v21. Summaries of continuous variables were reported as means and standard deviations. Summaries of categorical variables were reported as percentages. Independent samples *t*-tests or chi-squared tests were used to compare women who completed the study procedures with women who withdrew or were lost to follow up. Paired samples *t*-tests were used to examine changes over time to study variables. Wilcoxin Signed Rank Test was used to examine changes over time in data which was not normally distributed. As this was a feasibility study not powered to detect significant changes, Cohen's *d* was calculated to assess the effect sizes based on the mean differences between pre- and post-intervention.

10.3. Results

10.3.1. Missing data

Baseline questionnaires were completed by 33 participants. Follow up questionnaires were completed by 27 participants. Of the six women not completing follow up questionnaires, only one woman actually took part in the intervention. The remaining five women were lost to follow up and did not engage with the intervention. The baseline data was carried forward for the participants who did not complete the follow up questionnaires (n=6). Individual item missing data was very low (<5%) and was therefore replaced using mean substitution.

10.3.2. Recruitment and uptake

Figure 10.1 and Figure 10.2 show the recruitment and uptake rates from the previous study and from NHS sites. Invitations were sent to 99 participants from the previous quantitative

study described in Chapter 6. Of these, 53 responded, giving a 54% response rate. Of those that responded, only 36% were eligible (*n*=19). Reasons for ineligibility are shown in Figure 10.2. All 19 eligible participants consented into the study, giving a 100% uptake rate. Across five NHS sites, 158 patients were approached. Of these, only 26 were eligible (14%). The most common reason for ineligibility was being adherent (*n*=86). In addition to this, a further 150 women who were not prescribed tamoxifen were approached at the Guy's clinic. This was avoided at the remaining clinics, as it was possible to screen records and only approach women who were prescribed tamoxifen. Of the 26 eligible women recruited from NHS clinics, 76% (*n*=20) agreed to take part in the study. In addition to this, adverts were places on two Facebook groups and seven women responded to the study adverts. Of these, three women returned their screening questionnaires. All three women were eligible and were recruited into the study.

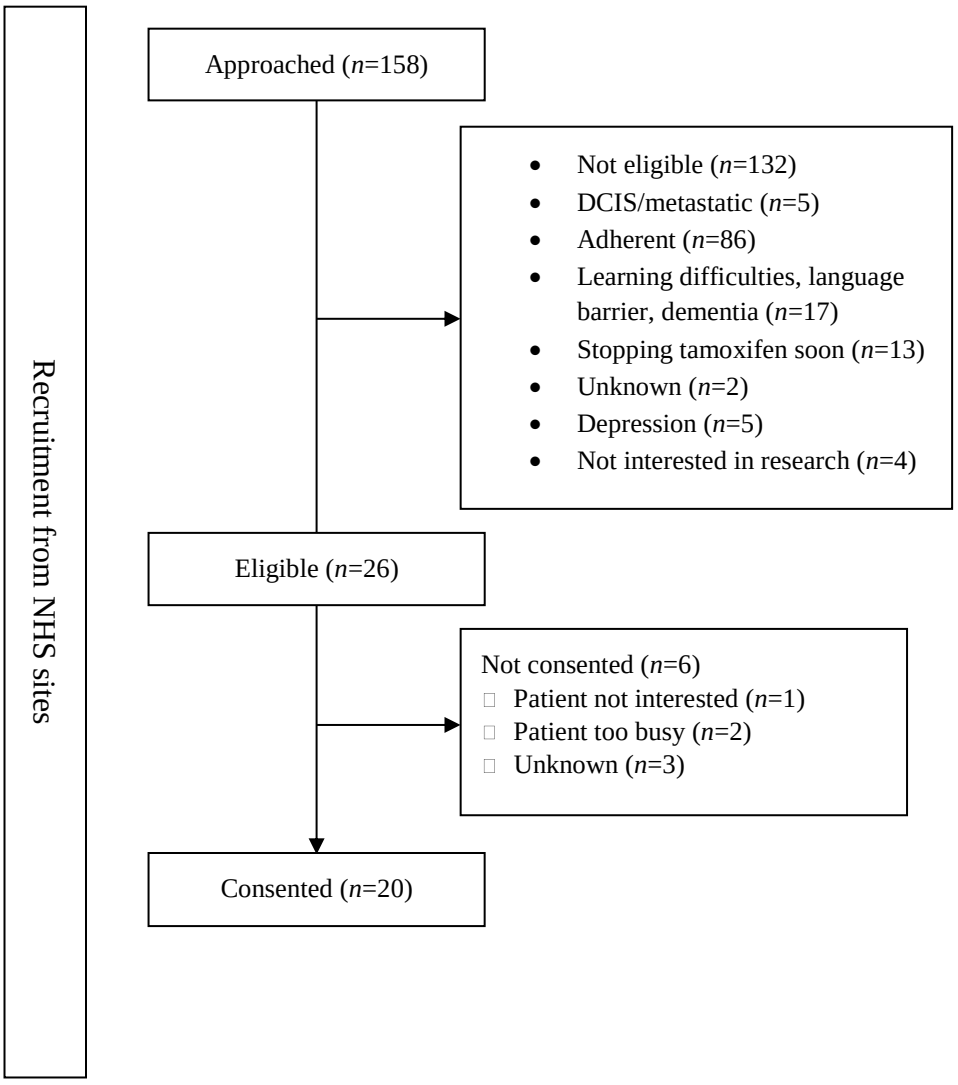

Figure 10.1 Flowchart showing recruitment from NHS sites.
DCIS=Ductal Carcinoma in Situ

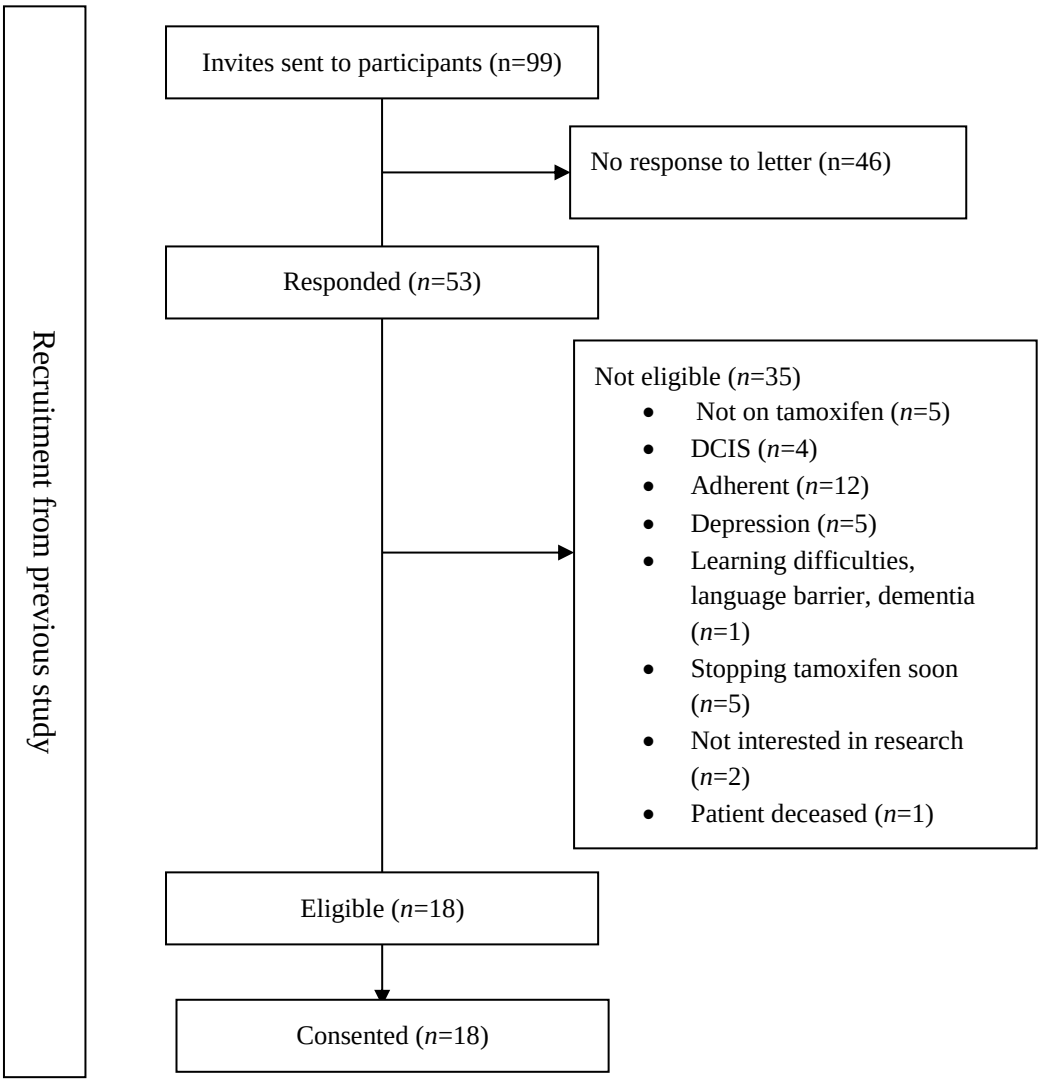

Figure 10.2 Flowchart showing recruitment from previous study.
DCIS=Ductal Carcinoma in Situ

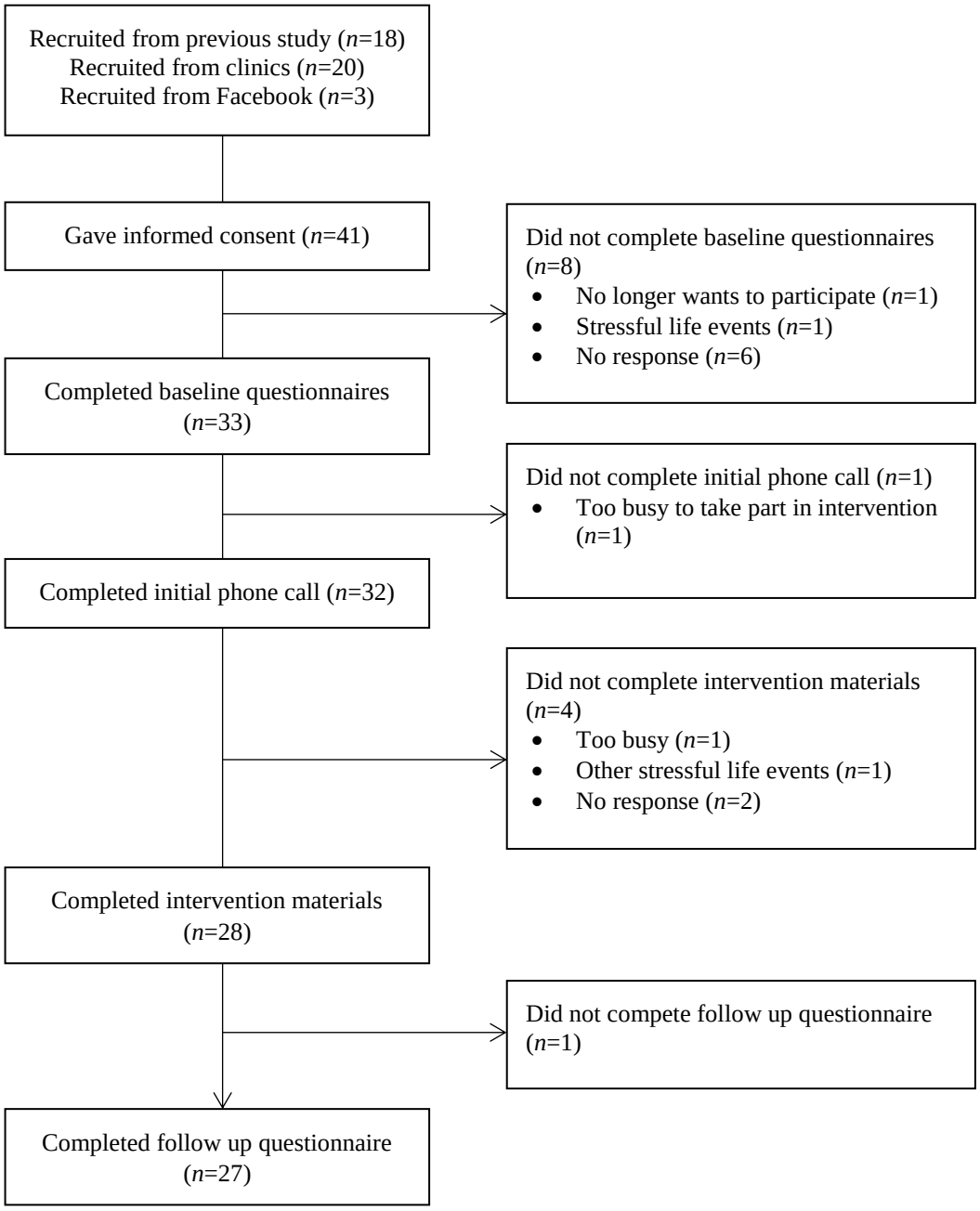

Figure 10.3 Flowchart showing participation retention through study

10.3.3. Study retention and participation

Forty one women consented into the study. Retention through the study is shown in Figure 10.3. Eight women did not complete their baseline questionnaires and did not continue with the study. Of the 33 women who did complete the baseline questionnaire (80%), 28 completed the intervention materials (68% of recruited sample, 85% of those beginning study procedures). Five women did not complete the intervention materials, four of whom were lost to follow up after completing the initial phone call and one who was too busy to

take part in the study. Reasons for attrition are shown in Figure 10.2. Follow up questionnaires were completed by 27 women (66% of total recruited sample, 82% of those beginning study procedures). Participants took on average seven weeks (*SD*=2.6) to complete the intervention procedures, but this ranged from two to 12 weeks. The qualitative interviews will provide insight into how many sections were completed by each woman. However, the telephone sessions conducted by the researcher showed that the women who took part in the intervention (*n*=28) were engaged and were happy to work their through the activities in the booklet. Women did not report any issues with completing the materials and only needed very low levels of support. The remaining five women were lost to follow up and it is not possible to tell whether they engaged with or adhered to the intervention.

Independent sample *t*-tests and chi-squared tests were run to identify any differences between women completing the full study and women who were not retained (Appendix J). Results showed that women who did not complete the study had lower MARS unintentional adherence scores at baseline (*M*=3.00, *SD*=0.00) than women who did complete the study (*M*=3.67, *SD*=0.6, *t*[26]=5.59, *p*<.001), indicating more unintentional non-adherence. No other differences were seen across groups.

10.3.4. Participant demographics

Participant demographics are shown in Table 10.1. Participant age ranged from 41 to 67, with a mean age of 51 (*SD*=6.1). The majority of women were White British (79%), were married or in a Civil Partnership (52%) and were employed (89%). Participants were mostly pre or peri-menopausal at diagnosis (76%) and had stage I (39%) or stage II (43%) breast cancer.

10.3.5. Baseline adherence rates

Higher scores on the MARS indicate higher adherence rates. Participants had to score below 25 in order to be eligible for the study. At baseline, mean MARS scores were 22.8 (*SD*=1.6). The MARS can also be separated into intentional and unintentional non-adherence. Intentional adherence is measured using four items, with a total score of 20 indicating full adherence. Mean scores were 19.3 (*SD*=1.4). Unintentional adherence is measured using one item, with a total score of 5 indicating full adherence. Mean baseline unintentional non-adherence scores were 3.5 (*SD*=0.6). At baseline, 30% of participants were intentionally non-adherent and 97% were unintentionally non-adherent. 21% of participants reported both intentional and unintentional non-adherence.

10.3.6. Side effects

Table 10.2 shows the side effects reported by participants at baseline. Hot flushes were reported by 91% of participants, with 52% reporting moderate or severe symptoms. High levels of night sweats (79%), changes in mood (79%) and joint pain (85%) were also reported. Around half of participants reported problems with vaginal health, fatigue or sleep difficulties.

10.3.7. Relationship between adherence and covariates at baseline

Pearson's correlations were run to identify if any covariates were associated with adherence scores at baseline. Higher MARS scores were associated with higher QOL (r=.42, p=.016), less intense side effects (r=-40, p=-.022), more positive necessity/concerns differentials (r=.51, p=.002), participants feeling more informed about treatment (r=.45, p=.008), having fewer tamoxifen consequences (r=-.45, p=.009) and attributing fewer symptoms to tamoxifen (r=-.51, p=.003). Higher baseline MARS scores were also associated with higher self-efficacy for managing insomnia (r=.51, p=.002) and changes in mood (r=.38, p=.030).

Table 10.1 Demographic characteristics of participants

	Completed baseline questionnaires (n=33)	Completed follow up questionnaires (n=27)
Age	41-68 M=51, SD= 6.1	42 – 67 *M=52, SD=6.3*
Ethnicity		
White British	26 (79%)	21 (78%)
Other	6 (18%)	5 (19%)
Missing	1 (3%)	1 (4%)
Relationship status		
Single	6 (18%)	5 (19%)
Married/Civil Partnership	17 (52%)	16 (59%)
Separated/Divorced	8 (24%)	6 (22%)
Co-habiting	2 (6%)	0
Job status		
Employed	29 (89%)	24 (89%)
Unemployed	1 (3%)	1 (4%)
Retired	2 (6%)	2 (7%)
Student	1 (3%)	0
Age left full time education		
16 or under	9 (27%)	8 (30%)
Over 16	24 (73%)	19 (70%)
Menopausal status at diagnosis		
Pre/peri-menopausal	25 (76%)	19 (70%)
Post-menopausal	6 (18%)	6 (22%)
Unsure	2 (6%)	2 (7%)
Breast cancer stage		
Stage I	13 (39%)	11 (41%)
Stage II	14 (42%)	12 (44%)
Stage III	6 (18%)	4 (15%)

Previous treatment		
Lumpectomy	20 (61%)	17 (63%)
Single Mastectomy	14 (42%)	12 (44%)
Double Mastectomy	1 (3%)	0
Chemotherapy	19 (58%)	14 (52%)
Radiotherapy	23 (70%)	17 (63%)
Hormone receptor status		
Positive	24 (73%)	20 (74%)
Negative	1 (3%)	1 (4%)
Unsure	8 (24%)	6 (22%)
Years since prescribed tamoxifen	3 (9%)	1 (4%)
<1 year	9 (27%)	7 (26%)
1-2 years	10 (30%)	10 (37%)
2-3 years	6 (18%)	6 (22%)
3-4 years	3 (9%)	2 (7%)
4-5 years	2 (6%)	1 (4%)
5+ years		
Comorbidities		
0	23 (70%)	17 (63%)
1	6 (18%)	6 (22%)
2	4 (12%)	4 (15%)

Table 10.2 Side effects reported by participants at baseline

	% experiencing symptoms	% experiencing moderate-severe symptoms
Hot flushes	91%	52%
Night sweats	79%	49%
Vaginal dryness, discharge or irritation	59%	28%
Fatigue	55%	-
Sleep difficulties	52%	-
Changes in mood	79%	36%
Joint pain	85%	48%

10.3.8. Changes to adherence

Table 10.3 shows the mean scores on the MARS pre and post intervention. There were no significant differences across time in the total MARS scale or the intentional scale. There was a small improvement in unintentional MARS scores but this did not reach significance (p=.058). The proportion of women classed as non-adherent fell from 100 to 91%. The proportion of women classed as intentionally non-adherent remained stable at 30%, but the percentage of unintentional non-adherence fell from 97 to 88%. Analysis was also conducted to assess the percentage of women who showed improvements on the MARS. Sixteen women (59%) showed no change in total MARS scores. Improvements in MARS scores were seen in seven women (26%) and reductions in MARS scores were seen in four women

(15%). One of these women discontinued tamoxifen during the study period at the suggestion of her Clinical Nurse Specialist, who recommended she took a break to assess whether her symptoms were caused by tamoxifen.

Table 10.3 Changes to adherence scores pre-and post-intervention

	Pre-intervention	Post intervention	Cohen's *d*	Comparison of pre-and post-scores
MARS total	22.8 (1.6)	23.1 (1.3)	0.15	p=.391†
MARS intentional	19.3 (1.4)	19.4 (1.1)	0.06	p=.786
MARS unintentional	3.5 (0.6)	3.7 (0.7)	0.31	p=.058 †
% Non-adherent	100%	91%	-	-
% Intentionally non-adherent	30%	30%	-	-
% Unintentionally non-adherent	97%	88%	-	-

Note. † Indicates that Wilcoxin Signed Ranks Test was used to compare means. Scores of 25 indicate total adherence. Scores of 20 indicate full intentional adherence. Scores of 5 indicate full unintentional adherence.

10.3.9. Changes to illness and treatment beliefs

BMQ necessity and concern scores increased and decreased respectively between baseline and follow up, but these were small effects and were not statistically significant (Table 10.4). There was, however, a significant increase in the BMQ differential score from baseline to follow up, with a small to medium effect size (t[32]=2.3, p=.031). There were very small non-significant changes to cure beliefs, risk of recurrence, tamoxifen consequences, breast cancer consequences, treatment control, emotional representations, causal beliefs or identity. Medium to large effect sizes were seen for improvements in personal control (t[32]=3.32, p=.002) and coherence beliefs (t[32]=4.36, p<.001).

10.3.10. Changes to side effects, quality of life and distress

Changes to side effects, QOL, distress and knowledge are shown in Table 10.4. HADS distress scores decreased significantly from pre to post intervention (t[32]=-3.03, p=.005), but the effect size was small. FACT-ES scores increased over time but the effect was very small and the differences were not statistically significant. The additional symptoms subscale of the FACT-ES was analysed independently to assess the extent to which the intervention improved symptom experience. Results showed that the symptom experience improved significantly over time, but the effect size was small (t[32]=2.10, p=.044).

Table 10.4 Changes to illness and treatment beliefs pre-and post-intervention

	Pre-intervention	Post-intervention	Cohen's *d*	Comparison of pre-and post- scores
Necessity	15.88 (3.1)	16.61 (3.2)	0.16	*p*=.199
Concerns	13.36 (4.5)	12.39 (3.8)	-0.23	*p*=.065
Necessity/concerns differential	2.76 (5.2)*	4.46 (4.3)*	0.36	*p*=.031
Cure	14.61 (2.2)	14.91 (2.6)	0.13	*p*=.339
Risk of recurrence	11.79 (3.6)	10.93 (3.4)	-0.17	*p*=.082
Tamoxifen consequences	11.97 (4.4)	11.42 (4.0)	-0.13	*p*=.198
Breast cancer consequences	13.61 (3.2)	13.21 (3.1)	-0.13	*p*=.196
Personal control	13.85 (2.4)**	14.88 (2.1)**	0.46	*p*=.002
Treatment control	15.24 (2.2)	15.42 (2.0)	0.06	*p*=.634
Coherence	13.88 (3.7)***	16.51 (2.7)***	0.58	*p*<.001
Emotional representations	14.36 (4.0)	14.33 (4.3)	-0.01	*p*=.953
Cause: psychological attributions	3.24 (0.9)	3.23 (1.0)	0.02	*p*=.935
Cause: health behaviours	3.51 (0.5)	3.58 (0.5)	0.15	*p*=.362
Cause: hormonal influence	4.31 (0.7)	4.34 (0.7)	0.05	*p*=.712
Symptoms attributed to tamoxifen (identity)	7.03 (5.3)	7.36 (5.1)	0.06	*p*=.589
Distress	14.55 (8.5)**	12.63 (8.0)**	-0.23	*p*=.005
Quality of life total	132.55 (28.5)	135.03 (25.8)	0.09	*p*=.188
FACT-ES Symptom score	59.15 (14.0)*	61.15 (12.6)*	0.15	*p*=.044
Self-efficacy for managing HF	68.48 (24.8)	71.21 (23.0)	0.08	*p*=.519
Self-efficacy for managing NS	69.09 (26.7)	71.81 (19.9)	0.12	*p*=.472
Self-efficacy for managing leg cramps/joint pain	59.09 (22.4)*	68.79 (22.7)*	0.31	*p*=.020
Self-efficacy for managing vaginal health	62.42 (26.1)***	74.54 (21.7)***	0.51	*p*=.001
Self-efficacy for managing fatigue	53.94 (28.6)***	65.15 (26.0)***	0.41	*p*=.001
Self-efficacy for managing insomnia	55.03 (28.6)*	69.38 (23.0)*	0.40	*p*=.007
Self-efficacy for managing changes in mood	50.64 (29.1)	58.79 (25.5)	0.30	*p*=.073
Extent to which participants feel informed	15.30 (3.0)**	17.03 (2.5)**	0.46	*p*=.004
SIMS	9.39 (4.5)**	11.48 (4.0)**	0.35	*p*=.007

Note. SIMS. Satisfaction with Information about Medicines Scale. Higher symptom scores indicate reduced impact of side effects. * Indicates a significant difference at $p<0.05$, ** indicates a significant difference at $p<0.01$, *** indicates a significant difference at $p<0.001$

Significant improvements were seen in women's self-efficacy to manage leg cramps/joint pain (*p*=.020), vaginal health (*p*=.001), fatigue (*p*=.001) and insomnia (*p*=.007), with a large effect size for improving vaginal health. A small improvement was seen for self-efficacy for managing changes in mood. However, only very small non-significant changes were seen to self-efficacy to manage hot flushes, night sweats and changes in mood. The extent to which participants felt informed about treatment (*t*[32]=3.14, *p*=.004) and their satisfaction with information about medications also increased significantly from baseline to follow up (*t*[32]=2.88, *p*=.007), with medium to large effect sizes.

10.4. Discussion

This chapter described the initial acceptability and feasibility testing of a psychoeducational self-management intervention for women prescribed tamoxifen. This was the first intervention designed to improve adherence in BCS taking tamoxifen. The aims of the intervention were to improve adherence through a series of key mechanisms; improving knowledge, addressing the necessity/concerns differential, reducing the impact of side effects, providing a routine for medication taking and modifying any unhelpful illness beliefs. The aim of the pilot study was to assess the acceptability and feasibility of the intervention prior to a larger scale RCT being carried out.

This pilot data suggests that a larger scale RCT would be feasible in this population. Reasonable response rates were seen from study advertisements and uptake from eligible women was high, especially compared with similar self-management interventions (Bourmaud et al., 2015; Foster et al., 2016; Lee et al., 2014). However, a large proportion of women did not meet the inclusion criteria for the study, with the main reason for ineligibility being high levels of adherence. This low rate of eligibility may present a barrier for recruitment in future studies. Non-adherent women may be less likely to attend follow up clinics, which may account for the low number of non-adherent women identified. Therefore, future trials may benefit from advertising across a range of sources including support centres and online support groups. In addition to this, many women were not eligible due to the fact that they were taking an Aromatase Inhibitor (AI) instead of tamoxifen. Whilst there are some differences between tamoxifen and AIs, there are many similar issues associated with both drugs, as described in Chapter 1. Therefore, future research could benefit from extending the intervention to be suitable for women on both tamoxifen and AIs. Furthermore, although many women in clinic were not eligible due to high rates of adherence, they expressed a strong desire to participate in the intervention due to wanting to improve their side effects. Therefore, the intervention could also be applied to improving QOL and side effects in adherent women with the aim of preventing the non-adherence and non-persistence that occurs over time, as shown in Chapter 3 and Chapter 8.

The feasibility data also showed that only two thirds of the women recruited were retained to the end of the study. However, of the thirteen women who were lost to follow up, only five women completed the baseline questionnaires and were sent the intervention materials. The retention rate based on the proportion of women who received intervention materials was higher (81%). This suggests that once women engage with the intervention they are motivated to complete the materials, indicating good acceptability. However, it should be noted that five women were sent the intervention materials but did not engage with the

study. This suggests that the self-management nature of the intervention may not suit everyone, and that some participants may need additional support. Unfortunately, it was not possible to interview these women to ascertain why they did not complete the study, as the researcher could not reach them. Women who did not take part in the full intervention had significantly lower baseline unintentional adherence scores than women who completed the study, suggesting they were more non-adherent and therefore could have benefited more from the intervention.

Nonetheless, the intervention appears to be acceptable and feasible in around two thirds of women entering the study, and around 85% of women who received the intervention materials. Qualitative interviews are being carried out with women after the intervention which will provide further details on acceptability of the intervention, but it was not possible to analyse these within the time frame of the PhD. However, the quantitative data shows promise for future research. Women did not report issues with any part of the study or intervention procedures.

The main aim of the study was to assess acceptability and feasibility of the intervention, and the study was not powered to detect differences in other outcomes. Despite this, some significant changes were seen during the intervention period. The necessity/concerns differential became significantly more positive from pre- to post-intervention. This suggests that women have begun to weigh up tamoxifen more favourably, which was a key aim of the intervention materials. Whilst the effect size was small, this improvement has important implications, as more positive necessity/concerns differentials were associated with decreased odds of non-adherence over the longitudinal study, and were also correlated with baseline adherence in the current study. This suggests that improving the necessity/concerns differential may cause women to become more adherent over time.

Whilst the necessity/concerns differential improved significantly, no differences over time were seen to treatment control. Interestingly, however, personal control did increase significantly from pre- to post-intervention, with a medium effect size. The intervention provided information and diagrams aimed at improving beliefs around the extent to which tamoxifen could control the risk of recurrence, so it is surprising that treatment control did not increase. However, scores on treatment control were higher at baseline than scores on personal control which might explain the lack of improvement in this variable. Participants may also perceive that taking tamoxifen is something they can do personally to control their risk, which would explain why perceptions of personal control increased significantly. Studies have shown some overlap and cross-loading between the constructs of personal and treatment control, which was supported by a strong correlation between constructs in the

factor analysis in Chapter 5 (Moss-Morris et al., 2002). However, the intervention materials also provided information around the effects that exercise can have on risk of recurrence, which may be responsible for the improvements in personal control.

Coherence beliefs increased significantly after the intervention, as did the extent to which participants felt informed and their satisfaction with information about medication. These were all medium to large effects. These improvements are in line with the aims of the intervention. The extent to which participants felt informed about treatment also correlated with adherence at baseline, suggesting that improvements in this variable could be associated with improvements in adherence. No improvements were seen to tamoxifen consequences over time, despite the intervention aiming to reduce the impact of side effects.

The intervention also aimed to improve participants' ability to manage their side effects, with the potential for reducing the intensity of side effects. Results showed that side effect intensity improved, as did self-efficacy for managing several symptoms, including fatigue, insomnia and vaginal health. Whilst there were medium sized effects for improvements in self-efficacy, the improvement in side effects was small. Results suggest that the Cognitive Behavioural Therapy (CBT) strategies for managing fatigue may have been beneficial in this population, supporting previous RCTs (Gielissen et al., 2007; Moss-Morris et al., 2012; van Kessel et al., 2008). However, self-efficacy for managing Hot flushes or Night sweats (HFNS) did not improve significantly in the study, despite the inclusion of CBT strategies which have shown to be effective in BCS (Mann et al., 2012). This is particularly troubling as results showed that a large proportion of participants experienced HFNS, and that around half of participants reported moderate to severe symptoms. Participants may need more help to engage with the CBT strategies for HFNS. The qualitative interviews will provide useful information as to whether women read and engaged with these sections.

These improvements to symptom management are important as they likely improve patient's day to day lives, as well as having the potential to improve adherence. Side effects have been shown in the previous chapters to be a driver for non-adherence, and therefore improving side effect experience could lead to later improvements in adherence. The longitudinal analysis showed that side effects may have more of a knock-on effect on adherence, which was supported by research by Corter (2013). Therefore, there may be a delay before improvements in side effects result in improvements in adherence. The improvements in self-efficacy for managing symptoms are also particularly important, as this variable was correlated with adherence in the baseline analysis. Furthermore, studies have shown that non-adherence may be related more to the difficulty of handling side effects, rather than the presence or frequency of side effects (Richardson et al., 1988). In

women with breast cancer, greater self-efficacy for coping with symptoms mediated the relationship between physical symptoms and impact on wellbeing (Liang et al., 2016; Shelby et al., 2014). However, improvements in QOL were not seen in this study. In addition to improving symptom management, the intervention also improved ratings of distress, which was associated with non-adherence in the longitudinal analysis, but this was a small improvement.

Whilst improvements were seen in study variables which are related to adherence, no significant improvements in overall adherence were found, and four women became more non-adherent over time (15%). However, 26% of women showed improvements in their total MARS scores (*n*=7), which shows some positive impact of the materials. Furthermore, there was a small improvement in unintentional non-adherence scores. The lack of an improvement in intentional non-adherence may be due to several factors. Firstly, the sample recruited may have been too adherent at baseline to detect any improvement. Mean intentional non-adherence scores were 19.2, which is close to the maximum score of 20. Efforts were made to only recruit women who were non-adherent, but this did not specify intentional or unintentional non-adherence. Furthermore, the cut off for non-adherence was high, and women only had to select that they "seldom" forget their medication in order to be eligible. Therefore, there may not be much room for improvement in these women. Mathes et al. (2014) reviewed interventions to improve adherence and found that studies with high rates of baseline adherence were less likely to find improvements in adherence. Secondly, the MARS may not be sensitive to changes in adherence, especially across this relatively short follow up period. The wording on the questionnaire does not refer to a specific timeframe, and therefore, in the follow up questionnaire, participants may be answering based on the medication taking behaviour both pre-and post the intervention. Questionnaires with a specific time-period may be more suitable at demonstrating change over time (Garfield, Clifford, Eliasson, Barber & Willson, 2011). Future trials could benefit from using a different measure of medication adherence.

An alternative explanation is that the intervention did not result in changes in intentional non-adherence. It may be that the changes in key mechanisms of adherence, such as necessity/concerns differential, will lead to later improvements in adherence rates. Furthermore, the longitudinal analysis in Chapter 8 showed that adherence rates decreased significantly between baseline and three months. Therefore, the fact that adherence did not decrease across the intervention is a positive finding. There was a small improvement in unintentional non-adherence, which may improve over as time as women continue to implement the strategies they learnt during the intervention. The qualitative interviews may give more insight into any changes to medication taking post the intervention.

Previous interventions for Hormone Therapy (HT) adherence have shown that educational materials can improve knowledge and satisfaction about information, but these studies did not investigate changes in adherence (Bourmaud et al., 2016; Heisig et al., 2015). As discussed in Chapter 9, educational materials alone are not sufficient to improve adherence rates (Costa et al., 2015; Sabate, 2003) and several studies have shown that educational materials do not improve adherence to AIs (Hadji et al., 2013b; Neven et al., 2014; Ziller et al., 2013). However, these studies simply aimed to provide information and they did not specify how they developed the intervention. The current intervention improves on these previous studies. Results show that by following a rigorous, theory based procedure for developing interventions, it is possible to elicit changes in key factors that have previously been shown to relate to non-adherence, and to show small improvements in non-adherence rates.

The improvements in treatment beliefs and knowledge may be partly due to the inclusion of diagrams, as previous studies have shown that visual representations and demonstrations of action can improve knowledge and medication beliefs (Jones et al., 2016; Karamanidou et al., 2008). The results also support two previous studies showing that providing information can result in changes to illness and treatment beliefs (O'Carroll et al., 2013; Petrie et al., 2012). Both of these studies also found improvements in adherence, which were not seen in the current study. However, these studies included a longer follow up period which may have allowed for more change in adherence.

The intervention appears to be acceptable and feasible and has success in modifying several key variables. Low uptake and high attrition is a problem associated with self-management interventions, and yet uptake and retention were relatively high in this study compared with previous studies (Coffey et al., 2016). Future research should develop this intervention further, before testing it in a larger RCT. The current study did not compare the intervention to a control group which is a limitation of the study, as improvements cannot be conclusively attributed to the intervention.

Future developments to the intervention will be informed largely by the qualitative interviews. For example, the interviews will provide information on whether women engaged with the CBT for HFNS section, as improvements in management of these symptoms were not seen. There may be a need to increase support around this section. In addition to these modifications, the materials could be transferred to an online platform. Similar web-based self-management interventions have been well received by BCS (Foster et al., 2016; Kanera et al., 2016; van den Berg, 2015). These online interventions have several benefits over paper based materials, mainly related to the low cost and ease in which

they can be rolled out and implemented to larger numbers of women. Furthermore, they may be more convenient for participants, as the materials and activities are easy to access. The qualitative interviews will assess whether participants in this study would be receptive to receiving an online intervention. Moving the materials online would also allow the content to be tailored to the individual, where an initial assessment may determine which sections the participant completes. Materials could also be tailored to both tamoxifen and AIs, with participants only being shown information which is relevant to them. Tailoring intervention materials has been suggested as a potential for improving the efficacy of adherence interventions (Horne et al., 2005; Hugtenburg et al., 2013). As high baseline levels of adherence have been shown to affect efficacy of interventions, future studies may benefit from recruiting women with lower rates of adherence.

Whilst developing the intervention further, efforts need to be taken to engage women who have been shown to be at high risk of non-adherence in the previous studies, such as women who are younger, who are working and who are from minority ethnic groups. There is a need to tailor intervention content to ensure that these women are supported and that the intervention is relevant to women at the highest risk of non-adherence.

To conclude, this study has shown that a self-management psycho-educational intervention booklet appears to be acceptable and feasible in this population and has shown success in improving medication beliefs, side effect management, distress, personal control and knowledge. This shows the importance of using a rigorous, theory-based process to develop interventions. Whilst no significant improvements were seen to adherence over the study period, there was a small improvement to unintentional non-adherence, and larger improvements were seen in variables which have been shown to predict adherence. Therefore, there is potential that adherence rates will improve. Future research should develop this intervention further before trialling it in a larger powered RCT. The intervention could also be applied to adherent women who are struggling with side effects.

11. Overall discussion

11.1. Chapter overview

The aim of this chapter is to provide a summary of the results described in Chapters 3 – 10. After summarising the results, novel contributions to the literature and theoretical and clinical implications will be discussed. Strengths and limitations of the research will then be reviewed, followed by suggestions for future research and overall conclusions.

11.2. Summary of aims and main findings

The aims of this PhD were to identify barriers associated with tamoxifen adherence in Breast Cancer Survivors (BCS), using validated models of health behaviour, and to develop an intervention to support BCS taking tamoxifen. These aims were achieved through a series of empirical studies described in Chapters 3-10. The main findings across the studies are summarised below.

High rates of non-adherence were identified, with more women reporting unintentional than intentional non-adherence. The longitudinal analysis showed that rates of both intentional and unintentional non-adherence increased significantly over time. Results suggest that these are somewhat distinct behaviours, with intentional non-adherence being predicted mainly by psychological factors and unintentional being predicted mainly by a small number of demographic factors. A key finding from the systematic review was that clinical and demographic factors were not consistent predictors of Hormone Therapy (HT) adherence or persistence. The quantitative analysis largely supported this, showing that the majority of demographic and clinical variables showed no relationship to adherence. However, women from minority ethnic groups and women who were younger and who were employed were more likely to be non-adherent in both the cross-sectional and longitudinal analyses. Longer time since initiation of tamoxifen was also associated with increased odds of non-adherence.

Both the qualitative (Chapter 4) and quantitative analysis (Chapter 7) showed that BCS taking tamoxifen experience a significant side effect burden which can have a major impact on quality of life (QOL). The systematic review showed an inconsistent relationship between side effects and adherence. This was supported somewhat by the qualitative study which showed that the impact of side effects on adherence was dependent on the patient's illness and treatment beliefs. If a woman felt that there was a strong benefit of taking tamoxifen and she was motivated to avoid a recurrence, she may continue taking tamoxifen despite her side effects. However, if she was less certain tamoxifen was necessary for her, then she may be less willing to tolerate these side effects. Women who described non-adherent behaviours

spoke about being conflicted between the importance of taking tamoxifen and the impact of the side effects. This relationship was supported by the quantitative analysis which showed that whilst side effects were associated with increased odds of non-adherence, this effect was no longer significant once the psychological variables were added to the models.

The Common Sense Model (CSM) and the Theory of Planned Behaviour (TPB) provided good explanation of non-adherence in the cross-sectional and longitudinal analyses. The ROC analysis in Chapter 8 showed that both models showed good ability at discriminating between adherent and non-adherent women, and neither model showed superior discrimination ability. In the cross-sectional analysis, a combination of both models explained more variance in overall non-adherence than either model alone. Key CSM variables associated with non-adherence across the studies included weaker beliefs in risk of recurrence, lower beliefs that health behaviours cause a recurrence, higher beliefs that stress causes a recurrence, less positive necessity/concerns differentials and higher tamoxifen consequences. From the TPB, predictors of non-adherence included lower Perceived Behavioural Control (PBC) and less positive attitudes towards tamoxifen.

In addition to the CSM/TPB variables, several other modifiable variables were associated with non-adherence, including lower social support, which was associated with baseline non-adherence, and higher levels of distress, which were associated with increased odds of non-adherence over time. The systematic review showed that women who were treated by a specialist had higher odds of persistence than women who were treated in general care. This was supported by studies in the review showing that a more positive patient/physician relationship was associated with better odds of adherence.

As well as changes to adherence rates over time, results also showed changes to several illness and treatment beliefs, supporting the self-regulatory component of the CSM. Levels of side effects increased significantly across the twelve month follow up period, as did beliefs around risk of recurrence, causal beliefs, symptoms attributed to tamoxifen and necessity beliefs. Significant decreases over time were seen in breast cancer consequences, concerns, intentions, and attitudes.

Based on the results of the previous studies, a self-management intervention was developed to support patients with their tamoxifen treatment. The initial pilot results suggest that this intervention is acceptable and feasible. Improvements were seen in unintentional non-adherence, treatment beliefs, personal control, distress, side effect intensity, ability to manage side effects, coherence, knowledge of, and satisfaction, with information about tamoxifen.

11.3. Contributions to the literature

The research described above makes several novel contributions to the literature, as well as supporting previous research and theory. The key novel contributions are listed below:

- Unintentional non-adherence was reported much more frequently than intentional non-adherence, and was associated with unique determinants. Previous research in HT adherence has largely failed to differentiate between intentional and unintentional non-adherence, but these studies highlight the importance of understanding both types of non-adherence. Unintentional non-adherence tended to be associated with demographic factors, whilst intentional non-adherence was associated more with psychological factors. This was a novel finding which adds to the understanding of intentional and unintentional non-adherence, and provides insight into how to modify these behaviours.
- Previous research has shown high rates of HT non-persistence, but these studies did not remove women who may have been discontinued by their doctors. This current study provides important clinical information by showing that rates of non-persistence where intervention may be possible, are lower than previously thought.
- Chapter 7 highlights the significant side effect burden associated with tamoxifen. Little previous research has investigated the prevalence and severity of these symptoms. Over 80% of participants reported hot flushes or night sweats in the past week, and 60% of these reported moderate to severe symptoms. Intensity of side effects was maintained over time, which contradicts advice often given clinically that side effects will diminish over time.
- These studies contribute important information on the relationship between side effects and tamoxifen adherence. Previous research has been inconclusive as to whether side effects are related to non-adherence. These studies suggest that the extent to which side effects are related to non-adherence is dependent on the beliefs women hold about tamoxifen and their risk of recurrence. Some women are happy to tolerate side effects because they believe strongly in the necessity of taking tamoxifen. The same level of side effects may cause another woman to become non-adherent, if her necessity beliefs are weaker. This provides important information for designing future research in this area and for developing ways to improve adherence.
- The IPQ-BCS is an adapted and validated version of the Revised Illness Perceptions Questionnaire for use in BCS. This will be of use to researchers investigating illness perceptions in these patients.

- This was the first study to apply the CSM and TPB to medication adherence in BCS. Both models provided good explanation and prediction of non-adherence to tamoxifen over 12 months.
- The CSM nor the TPB provided similar prediction of overall non-adherence, and the combination of models provided better explanation of non-adherence than either model alone. This suggests that the models complement each other and that neither model is sufficient alone for understanding non-adherence, which provides important information for future research and for intervention design.
- The research highlighted several new modifiable variables which were associated with increased odds of non-adherence. This provides important information for designing interventions to improve adherence rates.
- No previous research has examined changes to illness perceptions in BCS taking tamoxifen. The results of these studies show that these illness perceptions are dynamic and they show significant changes across a 12 month period.
- The intervention described in Chapter 10 was the first study to develop and pilot a self-management intervention to improve adherence to tamoxifen. Whilst no significant differences were seen in adherence, improvements were seen in key variables relating to adherence, such as the necessity/concerns differential, side effects and the extent to which patients feel informed about treatment, and there was a small improvement in unintentional non-adherence.

11.4. Theoretical implications

As discussed in Chapter 2, the CSM and the TPB have received large amounts of research interest and have shown success at predicting non-adherence in a range of conditions. However, no research has applied these models to medication adherence in breast cancer. The results from these studies have important theoretical implications for the TPB and the CSM. Results suggest that both models provide good explanation of non-adherence and are able to discriminate well between adherent and non-adherent women.

11.4.1. The Common Sense Model of Illness Representations

The CSM assumes that individuals will attempt to solve or control any health threat or illness they are faced with, and that the coping strategy used will depend on the way the individual perceives the illness or health threat. Within this framework, tamoxifen adherence can be conceptualised as a coping behaviour which is carried out to control the threat of a breast cancer recurrence. Following from this, the CSM would assume that whether someone adheres to tamoxifen is dependent on their illness perceptions or medication

beliefs. This was supported by the current results, as baseline illness and treatment perceptions could predict non-adherence over a 12-month period. In addition, cross-sectional analyses showed that CSM variables could explain up to 26% of the variance in non-adherence.

Women who had higher tamoxifen consequences had increased odds of non-adherence at baseline and over the 12 month follow up period. The tamoxifen consequences variable was created during the modification of the IPQ-BCS and it represents a different construct to the original *illness consequences* variable, as it measures consequences associated with the medication rather than the illness. The CSM assumes that an individual with high illness consequences will be motivated to adhere to their medication to reduce these consequences. However, higher *tamoxifen consequences* were associated with lower odds of adherence in this study. This is likely because if the medication has large consequences on a patient's life, they may be less motivated to take it. This was also supported in the qualitative study, with women discussing the impact of the side effects on their QOL as a motivator for non-adherence or non-persistence. Some women described side effects which prevented them from working or which impacted on their relationships with friends or family. Higher breast cancer consequences at baseline were also associated with increased odds of becoming non-adherent over time. This shows that the perceptions women hold about their previous breast cancer can still affect their health behaviour up to one year later. However, the relationship between breast cancer consequences and adherence was not significant in the multivariate analysis.

Higher perceptions around risk of recurrence were associated with increased odds of non-adherence in the cross-sectional analysis, but not in the longitudinal analysis. This was a new variable added to the IPQ-BCS, and the current results support its predictive utility. It makes theoretical sense that women who believe more strongly that they will have a recurrence will be more likely to be adherent, in an attempt to control this risk. This was also supported in the qualitative study, with avoiding a cancer recurrence being a key motivator for taking tamoxifen. Interestingly, causal beliefs were also related to non-adherence. In the cross-sectional analysis, beliefs that psychological stress causes a recurrence were associated with increased odds of intentional non-adherence, and believing that health behaviours cause a recurrence was associated with decreased odds of intentional non-adherence. This suggests that if women perceive that a recurrence is caused by factors outside of their control, such as stress, they are less likely to engage in behaviours to control the risk of recurrence, such as taking tamoxifen. These results support the findings of Jessop & Rutter (2003) who found that attributing asthma to external causes was associated with lower odds of adherence.

Similar relationships were seen between causal beliefs and adherence in the longitudinal analysis, but these did not reach statistical significance.

Attributing more symptoms to tamoxifen was associated with decreased odds of non-adherence over the 12 month follow up period. However, in the separate analysis for intentional non-adherence, attributing more symptoms to tamoxifen was associated with increased odds of non-adherence. Previous studies have found no relationship between symptom attribution and HT adherence (Corter, 2013; Walker et al., 2016). Therefore, more research may be needed in order to understand the relationship between attributing symptoms to tamoxifen and adherence.

In both the cross-sectional and longitudinal analyses, illness perceptions were better able to explain intentional than unintentional non-adherence. Intentional non-adherence was predicted by higher tamoxifen consequences, more symptoms attributed to tamoxifen and less positive necessity/concerns differentials. In addition to this, treatment control, breast cancer consequences and beliefs that psychological stress caused a recurrence were all associated with intentional non-adherence at $p<0.10$. The proportion of women categorised as intentionally non-adherent was quite small, and these effects may have become significant given a larger sample size. That these variables were associated with intentional non-adherence more than unintentional is in line with theoretical assumptions of the CSM. The model describes individuals carrying out deliberate and intentional actions in order to control a health threat and should therefore be better able to predict someone deliberately skipping doses than someone simply forgetting. However, there were some associations between unintentional non-adherence and illness/treatment beliefs in the longitudinal analysis, which supports previous research showing some overlap between intentional and unintentional non-adherence (Molloy et al., 2014).

No significant relationships were seen between emotional representations and adherence, in contrast to previous studies showing a relationship for these variables (Ross et al., 2004; Van der Have, 2016; Zugelj et al., 2010). These results suggest that the cognitive processing system may be more relevant to tamoxifen adherence than the emotional processing system. Whilst emotional representations around risk of recurrence were not associated with adherence, the perceived risk of recurrence was, suggesting that the cognitive perception of the risk is more important than patient's emotional responses to this risk. However, this could be due to measurement issues of the emotional representations construct, which was adapted in the IPQ-BCS.

This was the first study to apply the CSM to medication adherence in BCS. Overall, the qualitative and quantitative results provide support for the CSM and suggest that it is a

useful framework for understanding and predicting medication adherence. This suggests that interventions based on CSM constructs may be effective at improving medication adherence in this population. These results are contradictory to the conclusions of two recent meta-analyses, which found weak relationships between illness perceptions and adherence to self-management behaviours, concluding that the CSM was not a good framework for adherence (Aujla et al., 2016; Brandes & Mullan, 2014). The poor results in the meta-analyses may be due to the authors combining results across conditions and health behaviours, and failing to include medication beliefs. Some illness perceptions in this study showed no relationship with adherence. However, the CSM does not assume that all illness perceptions will be relevant in every condition or health behaviour, and this is not therefore a criticism of the theory. As well as supporting the predictive ability of illness perceptions, the results from these studies also support the self-regulatory nature of the model, as several illness perceptions were shown to change over time. For example, causal beliefs increased over time, which may be the result of new information from the media or significant others. Breast cancer consequences decreased over time, which suggests that as women move further away from their breast cancer treatment they perceive it to have less of an impact on their lives. Furthermore, the intervention described in chapters 9 and 10 was able to modify several of these illness and treatment beliefs through enhanced education.

The current results also provide support for the necessity/concerns framework, by showing that medication beliefs at baseline predicted later non-adherence. Previous research in HT adherence has shown mixed results, with some studies showing that medication beliefs were associated with adherence or persistence (Brett et al., 2016; Bright et al., 2016; Grunfeld et al., 2005; Arriola et al., 2014; Stanton et al., 2014) and others showing no significant effects (Bender et al., 2014; Friese et al.. 2013; Walker et al., 2016). The lack of effects in previous studies may be due to methodological weaknesses, such as using non-validated questionnaires or having very high rates of adherence. Most of the studies in the systematic review measuring beliefs were of low to moderate quality. Furthermore, the current study used the differential between necessity and concerns, whereas the previous studies have all utilised the individual scales. As the qualitative study in Chapter 4 clearly described a process of weighing these beliefs up against each other, it was felt that the differential would be a stronger predictor than either necessity or concerns alone. A woman may have very strong concerns about taking tamoxifen, but as long as her necessity beliefs are also high, she may remain adherent. The necessity/concerns differential attempts to capture both these elements, which explains why it may perform better than the individual components alone.

Previous research has been inconclusive as to the extent to which medication beliefs predict both intentional and unintentional non-adherence. Several studies have shown that

medication beliefs were only predictive of intentional non-adherence (Clifford et al., 2008; Wroe & Thomas, 2003; Wroe, 2002). However, others have shown that these beliefs also predict unintentional non-adherence (Gadkari & McHorney, 2012; Unni & Farris, 2011; Wray et al., 2006). In the cross-sectional analyses, medication beliefs were only associated with intentional non-adherence. In the longitudinal analysis, the necessity/concerns differential predicted both intentional and unintentional non-adherence, but the effect on intentional non-adherence was larger. These results suggest that medication beliefs have a stronger effect on intentional non-adherence, but that they may also act on unintentional non-adherence, perhaps by reducing a patient's motivation to remember the medication.

11.4.2. The Theory of Planned Behaviour

The TPB has come under significant criticism in recent years, with critics accusing it of not accounting for much variance in health behaviour, of being a static model, for its focus on rational processes and for being less effective when used outside university students (Conner & Sparks, 2005; Sheeran, Gollwitzer & Bargh, 2013; Sneihotta et al., 2014). The results from these studies suggest that at least some of these criticisms may be unfounded. In a clinical population of BCS, the TPB showed good explanation of non-adherence and was able to differentiate between adherers and non-adherers.

Higher intentions to take tamoxifen were associated with decreased odds of non-adherence in the cross-sectional analysis, which supports the central tenant of the TPB. However, this variable was removed from the longitudinal analysis due to it being highly positively skewed. Subjective norms were not associated with adherence in either the cross-sectional or longitudinal analyses. This may be a measurement issue as the scale showed poor reliability in this sample. However, other studies have also found subjective norms to be a poor predictor of non-adherence, suggesting there may be an issue with the construct itself (Armitage & Conner, 2001; Chisholm et al., 2007; Kagee & van der Merwe, 2006; Lin et al., 2016). Ajzen & Fishbein (2004), however, stated that not all TPB factors would be significant in predicting all behaviours, so this should not necessarily be seen as a criticism of the model. Furthermore, the TPB assumes that subjective norms would act indirectly on behaviour through intentions, which was not tested in the current study.

Attitudes towards tamoxifen were not associated with non-adherence in the cross-sectional analysis. In the longitudinal study, however, more positive attitudes towards tamoxifen were associated with decreased odds of non-adherence at the intercept and reduced risk of becoming non-adherent over time, although these effects did not remain significant in the multivariate analysis. The only TPB variable significant in the multivariate LGM was PBC, with higher PBC being associated with a 62% lower risk of being non-adherent (OR=0.38,

$p<.001$). Similar results were seen for the prediction of both intentional and unintentional non-adherence. This is supported by previous studies showing that self-efficacy for medication taking, a similar variable to PBC, was associated with unintentional non-adherence in patients prescribed HT (Kimmick et al., 2015; Wouters et al., 2014).

Several researchers have criticised the TPB for its lack of predictive power (McEachan et al., 2011; Sneihotta et al, 2014). The results from this study provide some support for this criticism, as PBC was predictive of baseline non-adherence but was not predictive of non-adherence over the 12 month follow up period. This may be because changes to personal circumstances during the follow up period may have reduced the accuracy of baseline PBC. PBC refers to a patient's perception of their ability to perform a given behaviour, and it might not necessarily represent an accurate perception of this ability, especially regarding the ability to perform the behaviour one year later where unforeseen external factors may inhibit someone's ability to perform the behaviour. As greater accuracy of PBC is shown to be associated with improved predictive power (Sheeran, Trafimow & Armitage, 2003), this may explain why baseline PBC is unable to account for future adherence rates. Nonetheless, results suggest that PBC is an important factor in understanding tamoxifen adherence and intervening to improve adherence. As this factor is not covered within the CSM, this highlights the importance of considering multiple models of health behaviour.

Overall, the results highlight the utility of the TPB in understanding medication adherence; supporting previous studies showing similar results (Bane et al., 2006; Chisholm et al., 2007; Kagee & van der Merwe, 2006), and suggesting that some of the criticisms towards the TPB may be unfounded. However, the results show that there are issues with several of the constructs within the TPB, suggesting that the theory may benefit from improvements in measurement. The variable *intentions to take tamoxifen* was removed from analysis in the longitudinal study, meaning a large part of the TPB was not able to be tested. Furthermore, the strongest correlate of non-adherence, PBC, was not predictive of later non-adherence, which provides support for the criticism that the theory does not have predictive utility. Finally, TPB constructs were complemented by CSM variables, suggesting that the TPB alone does not provide a complete explanation of tamoxifen non-adherence.

11.4.3. Comparison of the CSM and the TPB

As discussed in Chapter 2, it was felt that focussing solely on TPB or CSM variables may provide insufficient explanation of adherence behaviour, and that combining elements from both models may present greater understanding of non-adherence. There are shortcomings associated with each model, which are likely overcome by the addition of variables from the

alternative model. For example, the CSM overlooks the ease or difficulty of actually performing a behaviour such as medication adherence. The TPB covers this but fails to consider the patient's cognitive or emotional representations of their illness. Results from these studies support these hypotheses, showing that the models complement each other and that neither model provided superior prediction of non-adherence. When deciding whether to adhere to tamoxifen, women appear to undergo a dual processing system, where they appraise both the medication taking behaviour itself (TPB), and how this fits with their perception of the medication and the associated illness (CSM). This supports previous research suggesting that the explanation of behaviour could be enhanced by use of both the CSM and the TPB (Hunter et al. 2003; Orbell et al, 2006; Sivell et al., 2011).

This suggests that future studies should consider using multiple models of health behaviour when predicting behaviours such as adherence. Only using one model as a framework may mean that important constructs are missed, resulting in poorer prediction of health behaviour. Researchers have suggested that integrating multiple models into a single framework may provide a more complete theory of behaviour change, resulting in more effective behaviour change interventions (Corda et al., 2010; Michie et al., 2008; Nigg & Jordan, 2005; Reid & Aiken, 2011). Whilst little research has compared models of health behaviour in this manner, it provides important information for intervening to improve adherence rates. The intervention described in Chapters 9 and 10 was developed by incorporating elements from both the CSM and the TPB. For example, activities were designed to improve participant's PBC as well as to address medication concerns and unhelpful illness perceptions. Whilst the intervention did not have a significant effect on adherence, there was a small improvement in unintentional non-adherence which may be significant in a larger trial over a longer time period. Furthermore, the intervention prevented women from becoming more non-adherent over time, which was seen over three months in the longitudinal study. Improvements were also seen to key variables associated with adherence, which suggests the intervention may have a later knock on effect on adherence. Therefore, future interventions to improve medication adherence or other health behaviours may benefit from incorporating elements from both theories.

Two previous studies have compared the CSM and the TPB in the prediction of health behaviour (Hunter et al., 2003; Orbell et al., 2006). Hunter et al. (2003) found that a combination of constructs from the CSM and TPB explained the most variance in the context of help-seeking for breast symptoms, providing support for the results shown here. Orbell et al. (2006) compared the models in women receiving abnormal cervical smear results. Results showed that TPB variables explained 42% of the variance in intentions to attend a follow up clinic, and addition of CSM variables only explained a further 4% of

variance. Further, CSM variables did not significantly improve the model fit for predicting clinic attendance. However, both models were important in distinguishing between those who attended all their appointments as scheduled after being prompted, or ceased attending. This contrasts with the results from the current study which suggests that both models were useful in predicting medication non-adherence. The reason for this inconsistency may be because in the colposcopy study, women did not yet have an illness and they may therefore not have formed strong perceptions around this illness. In this context, beliefs around actually carrying out the health behaviour, which are more salient in the TPB, are likely to be more relevant. Combining this with the results from the current studies suggest that CSM and TPB may complement each other within individuals who have already been diagnosed with an illness, but that the TPB may be more useful in healthy populations.

However, whilst these psychological models explained significant amounts of variance in non-adherence, there was still a large proportion of variance unexplained. This suggests there may be other key predictors which are not being captured by these models. Frameworks such as the COM-B and the Theoretical Domains Framework (Jackson, Eliasson, Barber & Weinman, 2014; Michie et al., 2008) have collated variables across different social cognition models. For example, the COM-B covers factors relating to capability (comprehension of disease, cognitive functioning, dexterity), opportunity (costs, social support, stigma) and motivation (mood, self-efficacy, illness/treatment beliefs). These frameworks were designed to facilitate the development of behaviour change interventions. Future research applying more constructs from these frameworks may enhance the explanation of tamoxifen non-adherence and may help identify future targets for intervention. However, these frameworks cover large numbers of constructs and guidance is not currently provided on how to operationalise some of the constructs.

The CSM and TPB were better at predicting and explaining intentional than unintentional non-adherence. As intentional non-adherence was reported much less frequently than unintentional non-adherence, this may reduce the clinical utility of the models. However, whilst less frequently reported, intentional non-adherence may be harder to intervene upon, and therefore understanding this behaviour could have great benefit in improving adherence rates. Furthermore, intentional non-adherence is more likely to lead to non-persistence, as non-persistence reflects an intentional decision. Therefore, reducing rates of intentional non-adherence may have more of an impact on persistence rates than reducing rates of unintentional non-adherence would.

11.5. Clinical implications

Around three quarters of all BCS are prescribed HT to reduce the risk of their cancer returning. Yet studies show that up to 50% of women do not take their HT as prescribed for the full duration, which is associated with increased risk of recurrence and mortality. There are over 150 women diagnosed with breast cancer every day in the UK, and incidence rates are projected to rise over the next twenty years (Cancer Research UK, 2016). Therefore, understanding this behaviour and developing ways to support women could have real clinical implications for the large numbers of women prescribed tamoxifen. The research identifies two main ways in which adherence rates in this population may be improved: by identifying women who may be at risk of non-adherence, and by developing ways to support these women and improve adherence rates.

Firstly, the research highlights several demographic variables which may be used to identify women who are at greater risk of non-adherence. These demographic variables often had a stronger effect on non-adherence than the psychological variables. For example, results suggest that women who are younger, who are not white and who are working are more likely to be non-adherent. Clinicians should identify these women early on in treatment and assess if they will need extra support in adhering to their medication. Whilst not tested statistically, it is possible that the reason both younger and employed women were more non-adherent is because they are more likely to struggle with side effects of tamoxifen. It may be hard for younger women to adjust to the symptoms of an early menopause, and for women in the workplace to manage their workload around fatigue or hot flushes. Therefore, providing extra support in managing side effects may be beneficial for these women. However, results show that these demographic variables are associated with unintentional rather than intentional non-adherence. This suggests that these women could benefit from support with managing their medication taking routine and remembering to take tamoxifen.

The psychological variables identified as predictors of non-adherence, such as the necessity/concerns differential, tamoxifen consequences and PBC, may also be useful to identify women at risk of non-adherence, by use of a screening questionnaire administered clinically. A short screening tool, administered near the beginning of treatment may be able to identify women who are at later risk of non-adherence, thus allowing clinicians to offer greater support to these women. The longitudinal results also showed that higher levels of distress were associated with increased odds of non-adherence across the follow up period. This has been seen in patients with breast cancer and across other long term conditions (DiMatteo et al., 2000; Grenard et al., 2011; Mausbach, Schwab & Irwin, 2015). Therefore, screening women for distress may also indicate women who are at risk of non-adherence.

Secondly, the results provide insight into how to intervene to improve adherence in this population. Based on the body of research described in Chapters 2-8, a self-management intervention was developed to support women taking tamoxifen. This intervention was trialled in a small pilot study which showed promising results. Uptake and retention were good which suggests the intervention may be acceptable and feasible for these women. In addition to this, improvements were seen in several key variables. There was a small improvement in unintentional non-adherence. The necessity/concerns differential improved, which is shown to be associated with lower risk of non-adherence. Coherence, satisfaction with information and the extent to which patients feel informed about treatment also increased. There were improvements in side effect intensity and ability to manage side effects, which are important clinically. It is not possible to eliminate side effects entirely, but empowering women to manage their side effects more effectively should reduce their impact on daily life, which may prevent women from discontinuing treatment. Future research needs to test the intervention in a larger powered RCT, but these pilot results are promising. The intervention is a self-management booklet and needs little input from researchers or clinicians. Therefore, it is low cost and has the potential to be scaled out and delivered widely. Future research should ensure that the intervention materials are tailored to women who are at higher risk of non-adherence, such as women who are younger or who are working.

These results suggest that intentional and unintentional non-adherence are relatively distinct behaviours, with unique correlates. Unintentional non-adherence was reported much more frequently and does not appear to be explained well by psychological variables. Therefore, as well as the more complex self-management intervention, simple interventions to help patients to remember to take tamoxifen may be effective in this population. These interventions would not address any psychological components but would act simply as a reminder for participants. For example, text message reminders have shown some efficacy in increasing adherence rates (Thakkar et al., 2016; Vervloet et al., 2012). In addition, a large study across Walmart pharmacies in the US found that the use of calenderised blister packaging for medications, where days are printed onto the pill packaging, was associated with increased medication adherence (Zedler, Joyce, Murrelle, Kakad & Harpe, 2011). Tamoxifen is not currently packaged with calendarized blister packaging, and this presents a scalable intervention with the potential to help hundreds of thousands of women.

Additional clinical implications include the importance of helping patients to manage their side effects. Chapter 4 and chapter 7 showed that women experience a significant side effect burden, and yet many women described a lack of support with side effects. Participants in the qualitative study discussed not receiving the emotional or practical support they felt they

needed. In some cases, women felt that they were dismissed by their healthcare team, which left them feeling unvalidated. Similar results were also found in a qualitative study of women prescribed HT (Verbrugghe et al., 2015). Interestingly, many women are told that their side effects will likely improve over time, and yet the analysis in Chapter 7 showed that symptom burden remains high across all five years of treatment. Furthermore, the perceived intensity of side effects also increased significantly over the twelve month longitudinal study. As side effects have been shown to increase risk of non-adherence, this highlights the need to ensure that women are supported throughout treatment with their side effects. Helping women to manage their side effects should have dual benefits of improving both QOL and tamoxifen adherence.

Side effects appear to have more of a knock-on effect, affecting later non-adherence rather than immediate non-adherence. This is supported by a similar study where HT symptoms assessed at baseline were a predictor of non-adherence at follow up, but symptoms assessed at follow up were not (Corter, 2013). This suggests that women may be attempting to manage and cope with their side effects for some time before they consider non-adherence. This was supported by the quotes from women in the qualitative study who were weighing up the costs and benefits of treatment and trying to make a decision as to whether to continue treatment. Clinically, this suggests that there is potential to intervene once women experience symptoms, and to prevent these symptoms from leading to later non-adherence. Intervening early is particularly important, as both side effect intensity and rates of non-adherence increase significantly over time.

11.6. Strengths and limitations

Limitations relating to specific studies are discussed in the relevant chapters. Limitations relating more broadly to the body of work are discussed below.

One main limitation with the research is the assessment of medication adherence, which was carried out using the Medication Adherence Rating Scale (MARS). Self-report measures are known to over-estimate adherence rates and may not always provide good concordance with objective measures (Berg & Arnsten, 2006; Bruxvoort et al., 2015; Ziller et al., 2009). However, the MARS overcomes some of the limitations associated with self-report measures by utilising a validated scale, using optimised question response formats and by utilising non-judgemental statements to normalise non-adherence (Horne et al., 2001; Stirratt et al., 2015). Furthermore, O'Carroll et al. (2013) found high correlations between MARS adherence and adherence measured using Medication Event Monitoring System (MEMS) in stroke survivors. A high cut off point of <25 was used when dichotomising non-adherence in

the quantitative analysis. This was chosen on the basis of previous studies and on recommendations that high cut offs help to balance out the over-estimation of adherence rates (Huther et al., 2013; Stirratt et al., 2015; Timmers et al., 2016; van der Laan et al., 2017). However, this high cut off may have led to inflated levels of non-adherence. Nonetheless, rates were comparable with other studies using pharmacy refill rates to assess HT adherence (Cheung et al., 2015; Hershman et al., 2010; Partridge et al., 2003). Furthermore, sensitivity analysis using a lower cut off on the MARS showed a similar pattern of predictors as in the main longitudinal analysis.

This same high cut-off was also used to screen women for eligibility to the intervention study. Despite improvements to study variables associated with non-adherence, no significant improvements in adherence were seen. This may be associated with an inability of the MARS to detect changes over time (Garfield et al., 2011). Future work on the intervention should consider using an alternative measure of adherence; should triangulate from multiple sources; or should consider a lower cut-off to allow for more room for improvement in adherence. However, there was a small improvement in unintentional non-adherence, which suggests some ability of the MARS to detect change over time.

Due to the limitations associated with different measurements of adherence, it has been recommended that the best approach is to triangulate from multiple sources (Lam & Freso, 2015; Lehmann et al., 2014; Sabate, 2003). However due to time and financial constraints during the PhD, it was not possible to take multiple measures of adherence. Taking less than 80% of the prescribed medication, as assessed with pharmacy refill rates, is associated with reduced survival in BCS taking tamoxifen. Unfortunately, it is not possible to determine if the levels of non-adherence reported here would be associated with poor clinical outcomes. Women who had higher rates of non-adherence at baseline were less likely to return their follow up questionnaires at 3, 6 and 12 months. This means the true rates of non-adherence are likely to be higher than the levels reported here. As non-adherent women were less likely to complete the follow up questionnaires, it is also likely that they would also be less likely to be recruited into the study. Therefore, there is a need to identify ways to engage and retain non-adherent participants, in order to better understand non-adherence. A further limitation is that it was only possible to predict adherence rates. Future research should extend these results to investigate predictors of tamoxifen non-initiation or non-persistence. Recruiting women at the point of being offered tamoxifen would allow for identification of predictors of non-initiation. Due to the low rates of non-persistence identified in this study, it was not possible to identify predictors of non-persistence. Extending the follow up for a longer period of time may have identified higher rates of non-persistence.

Whilst retention rates in the longitudinal study were quite high, there was some attrition over time, and this was found to be related to ethnicity, adherence rates, side effects, distress and age. This creates some risk of bias in the results, as the data is not missing at random. However, the fact that non-adherent women were less likely to return their questionnaires suggests that the non-adherence rates may actually be higher than what is reported here. Retaining these non-adherent women may have strengthened the relationships seen here between predictor variables and non-adherence.

A further limitation with the study is the lack of generalisability with regards to the ethnicity of the women in the quantitative analysis. Whilst this is somewhat typical of the population, as white women have significantly higher age standardised breast cancer incidence rates compared to other ethnicities (Jack, Davies, & Moller, 2009), the rates of other ethnicities in this study were very low. Furthermore, women who were not white were less likely to return their follow up questionnaires, which further reduces the generalisability of the results. Future research needs to look at ways to ensure that women from a range of different ethnicities and cultural backgrounds are properly represented. Results showed that women who were not white were less adherent to tamoxifen. This is consistent with studies showing worse clinical outcomes in women with breast cancer from minority ethnic groups (Chlebowski et al., 2005; Clegg et al., 2002; Eley et al., 1994). These poor clinical outcomes may be driven by health behaviours like non-adherence, by biological differences or by differences in socioeconomic status (Carey et al., 2006). Large, generalizable studies are needed to fully understand the effect of ethnicity on adherence. However, whilst there were issues with the ethnic diversity in the quantitative analysis, both the qualitative and the intervention studies provided more generalizable samples.

Whilst the cross-sectional analysis in Chapter 6 showed that the CSM and TPB were able to explain up to 46% of the variance in non-adherence, there were still large amounts of variance unexplained, especially with regards to unintentional non-adherence. Therefore it is likely that there are several important variables which were not assessed in the current study. One such variable might be the perceived quality of the patient/provider relationship, which showed some association with tamoxifen adherence in the systematic review. This relationship is also supported across studies in a range of long term conditions (Beach, Keruly, & Moore, 2006; Jackson et al., 2010; Haskard Zolnierek & DiMatteo, 2009). However, BCS in the UK are being moved to Open Access Follow Up, which replaces traditional regular follow up specialist clinics. Therefore, the patient/provider relationship may not be as relevant as in other conditions where patients receive regular follow up from a specialist. Another variable which might help to explain unintentional non-adherence is cognitive function. It stands to reason that women who are experiencing deficits in cognitive

functioning may find it harder to remember to take their medication daily. Several studies have supported this, showing increased non-adherence in patients with deficits in attention, mental flexibility or working memory (Hinkin et al., 2002; Stilley, Bender, Dunbar-Jacob, Sereika, & Ryan, 2010). This may be particularly relevant in BCS, as many women report poor cognitive functioning after chemotherapy or whilst taking tamoxifen (Castellon et al., 2004; Jim et al., 2012; Schilder et al., 2010). In an RCT of tamoxifen for prevention of primary breast cancer, odds of non-adherence were lower for women who showed better scores on measures of verbal memory (Klepin et al., 2014).

Another explanation for the unexplained variance is that the studies failed to assess the complete CSM or TPB. Static measures such as the Illness Perception Questionnaires have been criticised by developers of the CSM for failing to consider additional factors such as intra-individual variation and change, or unique illness contexts (Leventhal et al., 2016; Phillips et al., 2017). In addition to this, updates to the CSM have also stressed the importance of understanding planning processes and habit formation (Leventhal et al., 2016). Incorporating these variables may have enhanced the predictive ability of the model. Furthermore, it was not possible to fully test the appraisal and feedback loops inherent to the CSM. Likewise, issues with measurement of the TPB may have prevented the model from reaching its potential predictive power.

There were also limitations with the intervention, mainly relating to the lack of a control group. Randomised controlled trials are the gold standard for assessing the effectiveness of interventions, as they allow for identification of cause and effect between treatment and outcome. As the pilot study did not compare the intervention to an alternative treatment or wait list control, it is not possible to determine if changes are due to the treatment or to other factors. Future research should extend the pilot results and test the intervention in a larger RCT. A further limitation with the intervention is that the same researcher was involved in delivering the intervention and collecting follow up data. However, as the follow up data was collected by self-report questionnaires which were mainly carried out online, this is unlikely to have affected the results. To counter the potential influence of familiarity with the researcher, a second independent researcher carried out interviews with participants after completing the intervention to elicit their feedback.

There were also several strengths associated with the body of research. It was the first study to apply these psychological models to tamoxifen non-adherence, and to identify modifiable predictors in both a large cross-sectional study and a 12 month longitudinal study. The long follow up period allows for testing of causal relationships, which was largely lacking in previous studies. The majority of previous adherence interventions have not been effective,

and this has been linked to the lack of a theoretical framework and the failure to consider both intentional and unintentional non-adherence (Holmes et al., 2014; Horne et al., 2005). Therefore, the use of the CSM/TPB is a strength of the current body of research, as is the consideration of both intentional and unintentional non-adherence.

A further strength with the research is the robust statistical analysis. LGM is a valuable methodology which moves beyond traditional longitudinal analysis by modelling both fixed and random effects (Duncan, Duncan & Strycker, 2013; Hertzog, von Oertzen, Ghisletta & Lindenberger, 2008). The use of LGM allows for investigation of inter-individual differences in change over time and for identification of antecedents of change (Preacher , 2010). Another strength of the research is the mixed methodology; bringing together a range of different methodologies allows for clearer interpretation of results and for consistent patterns to be identified. Results seen in the cross-sectional analysis were strengthened by the results from the longitudinal analysis. Furthermore, the qualitative research in Chapter 4 helps with interpretation of the quantitative results and provides context for the body of research.

11.7. Future work

Several potential directions for future directions have been discussed in the sections above and in the relevant chapters. One of the most important avenues for future research would be to further develop and test the intervention, as described in Chapter 10. The pilot data shows promising results, but the study was limited by the lack of a control group. Future research should trial the intervention in an RCT. The materials may also benefit from being moved to an online platform, where they could be tailored to each participant. Furthermore, future research could consider trialling a modified version of the intervention to support adherent women who are struggling with side effects to prevent later discontinuation.

Future research should also consider variables which are missing from the current analysis, such as patient/provider relationship, habit strength or cognitive functioning. These variables may increase explanation of non-adherence and therefore suggest future avenues for intervention. Further research should also be undertaken to examine some of the relationships seen in this study. For example, women from minority ethnic groups and women who were employed had higher odds of non-adherence. In order to identify the best ways to support these women, more research needs to be conducted to understand the driving force of non-adherence in these populations. Qualitative research might provide interesting insights to help answer these questions.

Unintentional non-adherence was reported more frequently than intentional non-adherence but was not explained well by psychological variables. This suggests that more simple interventions based purely on reminders, and not on modifying beliefs, may be effective at improving adherence in this population. Whilst these kinds of intervention are likely only effective in women who are motivated to take their medication, they do show some promise and are relatively easy to design and implement. Future research should examine if these reminder interventions would have any efficacy in this population. In addition to this, future research could examine if there is any clinical utility to using psychosocial variables identified in this study as a screening tool to identify women at risk of non-adherence.

Finally, there is scope for future research around the models of health behaviour used in this study. Results suggest that the CSM and TPB complement each other well when explaining and predicting non-adherence to tamoxifen Therefore, future research could apply this combined CSM/TPB to medication adherence in other conditions. This may improve on other research using one of these models in isolation, and may provide important insights into intervention design. In addition to this, both models could also be explored in more detail. For example, within the CSM, there is scope to test feedback loops and causal pathways between illness perceptions, medication beliefs and health behaviour. Several studies have shown that illness perceptions may act indirectly through medication beliefs (Horne & Weinman, 2002; Ross et al., 2004), but this was not tested in the current study. Furthermore, cluster analysis has shown interesting results in identifying distinct clusters of illness perceptions (Harrison et al., 2014; McCorry et al., 2013a; Unni & Shiyanbla, 2016). Within the TPB, future research could test the hypothesised causal pathways between constructs, such as the prediction of intentions by attitudes, PBC and subjective norms.

11.8. Overall conclusions

The current body of research highlights the importance of understanding tamoxifen non-adherence and of intervening to improve adherence. The studies described show that non-adherence is reported frequently by patients and that reported rates of non-adherence increase over time. This was the first study to apply the CSM and TPB to non-adherence in BCS and it makes several novel contributions to the literature. Results show that non-adherence is a complex behaviour which is best understood by a combination of demographic factors and variables from the CSM and TPB. The models complemented each other well, which has theoretical implications which could be applied to medication adherence in other conditions. Key variables associated with non-adherence across studies include ethnicity, working status, medication beliefs, perceived risk of recurrence and PBC. Side effects were related to adherence but appear to be dependent on the patient's illness or

treatment beliefs. An important finding was that intentional and unintentional non-adherence appear to be relatively distinct behaviours with unique correlates.

The results from these studies have important implications for identifying those at risk of non-adherence and for intervening to improve adherence in this population. This was the first study to develop and pilot an intervention to improve adherence to tamoxifen. Initial pilot results are promising, suggesting the intervention is acceptable and feasible, and that it is associated with improvements in key mechanisms of non-adherence. Future research should develop the intervention further, perhaps on an online platform, and should test the intervention in a large RCT with the aim of improving quality of life and prognosis of breast cancer survivors.

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Appendices

Appendix A

Supplementary material for systematic review (Chapter 3)

Database	Dates	Search terms
Medline	1946 –18th April 2016	1. Medication Adherence/ 2. Patient Compliance/ 3. (adher* or complian*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. (persist* or discont*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 5. 1 or 2 or 3 or 4 6. Tamoxifen/ 7. tamoxifen.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 8. aromatase inhibitors/ 9. aromatase inhibitor*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 10. Endocrine therapy.mp 11. Hormon* therapy.mp 12. 6 or 7 or 8 or 9 or 10 or 11 13. Breast Neoplasms/ 14. Breast cancer*.mp 15. breast neoplasm*.mp 16. 13 or 14 or 15 17. 5 and 12 and 16 18. Limit 17 to female
Psychinfo	1806 –18th April 2016	1. Exp Treatment compliance/ 2. (adher* or complian*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] 3. Exp Treatment Termination/ 4. (persist* or discont*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] 5. 1 or 2 or 3 or 4 6. Exp Hormone therapy/ 7. tamoxifen.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] 8. endocrine therapy.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] 9. aromatase inhibitor*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] 10. hormon* therapy.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] 11. 6 or 7 or 8 or 9 or 10 12. Exp breast neoplasm/ 13. (breast cancer* or breast neoplasm*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] 14. 12 or 13

		15. 5 and 11 and 14 16. Limit 15 to female
Embase	1974 - 18th April 2016	1. Patient compliance/ 2. (persist* or discont*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 3. (adher* or complian*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 4. 1 or 2 or 3 5. Tamoxifen/ or tamoxifen.mp. 6. Aromatase inhibitor/ 7. Hormonal therapy/ 8. aromatase inhibitor*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 9. hormon* therapy.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 10. endocrine therapy.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 11. 5 or 6 or 7 or 8 or 9 or 10 12. Breast cancer/ 13. (breast neoplasm* or breast cancer*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 14. 12 or 13 15. 4 and 11 and 14 16. Limit 16 to female
Web of Science	Up to 18th April 2016	1. Adher* or complian* 2. Persist* or discontin* 3. 1 or 2 4. Tamoxifen 5. Aromatase inhibitor* 6. Hormon* therapy 7. Endocrine therapy 8. 4 or 5 or 6 or 7 9. breast cancer* or breast neoplasm* 10. 3 and 8 and 9
CINAHL	Up to 18th April 2016	1. (MH "Medication Compliance") OR (MH "Patient Compliance") 2. adher* or complian* or persist* or discontin* 3. 1 or 2 4. (MH "Tamoxifen") OR (MH "Aromatase Inhibitors") OR (MH "Hormone Therapy") 5. Tamoxifen OR Aromatase inhibitor* OR Hormon* therapy OR Endocrine therapy 6. 4 or 5 7. (MH "Breast Neoplasms") 8. Breast cancer* or breast neoplasm* 9. 7 or 8 10. 3 and 6 and 9

Appendix B

Patient documents used in the qualitative study

Patient Information Sheet Phase 1

REC reference number: 14/EM/1207

Investigating how women with breast cancer view Tamoxifen

We would like to invite you to take part in a research study conducted by King's College London and Guy's and St Thomas' Foundation NHS Trust.

The study will investigate women's experiences of Tamoxifen in breast cancer. Before you decide if you would like to participate, we will tell you why the research is being done and what it will involve for you.

One of our team will go over this information sheet with you and give you the opportunity to ask any questions. You will then be able to decide if you are interested in taking part in the study. If you would like more time to think about it, you can contact the researcher at a later date. The contact details are at the bottom of this form.

What is the purpose of the Study?

This study aims to understand what it is like to take Tamoxifen. We would like to find out about your experiences and perceptions of Tamoxifen. This is part of a larger study to identify factors associated with how women with breast cancer use Tamoxifen. The results from these studies will be used to design ways to support women on Tamoxifen. The research is being carried out as part of a PhD at King's College London.

Why have I been asked to take part?

We have asked you to take part in the study because we are interested in hearing from women who have been prescribed Tamoxifen. We are especially interested in speaking to people who are in their first few weeks or months of treatment. There will be around 20 – 30 women taking part in the study.

Do I have to take part?

It is up to you if you would like to join the study – you do not have to if you do not want to. If you are interested in taking part, we will call you in two days to arrange an interview. At the interview we will ask you to sign a consent form. You are free to change your mind and to withdraw at any time. This will not affect your standard of care.

What will the study involve?

The study will involve you taking part in an interview about your experience of taking Tamoxifen. The interview will be informal and will be one on one and face to face. You may also be interviewed over the telephone. It will last between 40 minutes and an hour. The researcher will have a list of topics that she would like to discuss but we are interested in *your* experience and so you are free to focus the discussion on what you think is important. The topics will include your experiences and perceptions of Tamoxifen. The researcher will also ask some general information about you and may collect clinical information about your breast cancer treatment. The interview will take place at a time and place to suit you and you will only be asked to meet once. We would like to record the interview using an audio recorder so that the researcher can fully concentrate on what you are saying. The recordings will be deleted once they have been typed up.

We will also ask you if you are happy to be contacted again in the future to review some questionnaires for us. This is completely voluntary. It would involve you reading over the questionnaire on the telephone with the researcher and sharing your thoughts.

Will I be reimbursed for my time?

We can reimburse you up to £10 for your travel costs.

Will my information be kept confidential?

Your personal information will be kept confidential. The interview will be recorded using an audio recorder, and the interview will be typed up. The recording will be deleted and the typed up interview will be made anonymous. Any personal details or identifiable information will be removed. Contact details will be stored separately in a locked filling cabinet. Only the researchers will have access to the data. The information will be kept securely at King's College London. The information will be destroyed five years after the research has finished. If you withdraw during the study your data will be destroyed. Data cannot be withdrawn once the results have been analysed and written up (June 2015). In the unlikely event of any risk such as self-harm or suicide risk, confidentiality will need to be broken. Your safety is very important. Both you and your clinical team will be made aware of the breach of confidentiality.

What are the possible disadvantages / benefits of taking part?

The risk of taking part is very minimal. You will only need to meet with the researcher once. This will be done at a time and place convenient to you. The interview will be conducted in a private place. The nature of the interview is unlikely to be sensitive. You are free to not answer certain questions if you find them distressing. There will be no direct benefits to you for taking part in this study. However, the results will provide more information about women's experiences with Tamoxifen. This will help improve the treatment of women with breast cancer in the future.

What if there is a problem?

If at any time during the interview you would like to stop then please inform the researcher and they will stop the interview immediately. If the interview raises any issues that you would like to discuss further, the researcher will be able to put you in contact with the relevant person. If you have a concern about any aspect of this study, you can speak to the Principal Investigator or any other researchers involved in the study. The contact details are at the bottom of this sheet.

What will happen to the results of the research study?

The results of this study may be published in scientific journals. You will not be identified in any report. Where quotes may be used, they will be completely anonymous. A report will be made available through Breast Cancer Campaign and a lay summary will be sent to participants.

Who has reviewed the study?

This study has been checked by Northampton Research Ethics Committee, an independent group of people, to protect your safety, rights, wellbeing and dignity.

How has the study been funded?

The study has been funded by Breast Cancer Campaign. It is part of a three year funded project to understand more about how women take Tamoxifen and how to improve Tamoxifen use.

Any further queries?

If you have any questions or concerns about the study, you may contact the following organisations

For independent advice on participating in NHS research:
Patient Advice and Liaison Service (PALS) - 0207 188 8803

For independent advice about making a complaint:
South London Independent Complaints Advisory Service (ICAS) – 0300 456 2370

For information from the researchers:

Miss Zoë Moon: zoe.moon@kcl.ac.uk 0207 188 9324 (Principal Investigator)

Dr Lyndsay Hughes: lyndsay.hughes@kcl.ac.uk 0207 188 9779

CONSENT FORM Phase 1

Title of Project: Investigating how women with breast cancer view Tamoxifen

Name of researcher: Zoë Moon

Please initial each box

1. I confirm that I have read and understood the information sheet dated 20/10/2014 (v2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. I understand that data cannot be withdrawn once the results have been analysed and written up (June 2015). ☐
3. I understand that relevant sections of my medical notes may be looked at by the research team and that research data collected during the study may be looked at by individuals from King's College London, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I agree that the interview may be audio recorded. ☐
5. I agree to be contacted in the future about follow up studies to this project. ☐
6. I agree to be contacted in future to discuss the development of a questionnaire. ☐
7. I agree to take part in this study. ☐

……	……
Patient's name	Patient's signature
Date: ……	
……	……
Researcher's name	Researcher's signature
Date: ……	

Appendix C

Patient documents used in the quantitative study

Patient Information Sheet Phase 2

REC reference number: 14/EM/1297

Investigating how women with breast cancer view Tamoxifen

We would like to invite you to take part in a research study conducted by King's College London and Guy's and St Thomas' Foundation NHS Trust.

The study will investigate women's experiences of Tamoxifen in breast cancer. Before you decide if you would like to take part, we will tell you why the research is being done and what it will involve for you.

One of our team will go over this information sheet with you and give you the opportunity to ask any questions. You will then be able to decide if you are interested in taking part in the study. If you would like more time to think about it, you can contact the researcher at a later date. The contact details are at the bottom of this form.

What is the purpose of the Study?

The purpose of the study is to understand what it is like to take Tamoxifen. We would like to find out how you feel about Tamoxifen and breast cancer. This is part of a larger study to identify factors associated with how women with breast cancer use Tamoxifen. The results from these studies will be used to design ways to support women on Tamoxifen. The research is being conducted as part of a PhD at King's College London.

Why have I been asked to take part?

We have asked you to take part in the study because we are interested in hearing from women who have been prescribed Tamoxifen. We are especially interested in speaking to people who are in their first few weeks or months of treatment. There will be around 520 women taking part in the study. We are interested in your thoughts and opinions, even if you have stopped taking Tamoxifen.

Do I have to take part?

It is up to you if you would like to join the study. If you are interested in taking part, we will ask you to sign a consent form. You are free to change your mind and to withdraw at any time. This will not affect your standard of care.

What will the study involve?

The study will involve you completing a series of questionnaires. The questionnaires have all been approved by the NHS research ethics committee. You will be asked about your experiences, thoughts and beliefs. The questionnaires should take around twenty minutes to complete. After completing the questionnaire you can either return it to the researcher or use the stamped addressed envelope provided to post it to the researcher free of charge. You can also complete the questionnaire online by accessing this link:

https://kings.onlinesurveys.ac.uk/tamoxifen

If you are within your first year of treatment, we will ask you to complete the questionnaires again in three, six and twelve months' time. This will allow us to see how your thoughts and experiences change over time. We will ask for your postal or email address so we can send you the follow up questionnaires. You can choose to receive an online questionnaire or a paper questionnaire with a stamped addressed envelope.

A group of patients will be asked to complete a subset of the questionnaire at two different time points. They will be asked to complete the questionnaire once when they consent to the study and once again two weeks later. This questionnaire should take five to ten minutes to complete.

Will my information be kept confidential?

Your personal information will be kept confidential. The questionnaires will be inputted into a computer. Only the researchers will have access to the computer which will have a password to protect all confidential files. Any personal details or identifiable information will be removed and contact details will be stored separately in a locked filling cabinet. The data will be kept securely at King's College London. It will be destroyed five years after the research has finished. Your contact details will be destroyed as soon as the study has finished. Data cannot be withdrawn once the results have been analysed and written up (December 2016). In the unlikely event of any risk such as self-harm or suicide risk, confidentiality will need to be broken. Your safety is very important. Both you and your clinical team will be made aware of the breach of confidentiality.

What are the possible disadvantages / benefits of taking part?

The risk of taking part is extremely minimal. You will only need to complete a questionnaire which can be done at home or in the clinic. The questionnaire has been used previously and should not cause any distress. There will be no direct benefits to you for taking part in this study. However, the answers that you give will provide the researchers with more information about Tamoxifen. This information will help improve the treatment of women with breast cancer in the future.

What if there is a problem?

If the questionnaire raises any issues that you would like to discuss further with a health professional, the researcher will be able to put you in contact with the relevant person. You are free to stop completing the questionnaire at any point. If you have a concern about any

aspect of this study, you can speak to the Principal Investigator, or any other researchers involved in the study. The contact details are at the bottom of this sheet.

What will happen to the results of the research study?

The results of this study may be published in scientific journals and at medical and psychological academic conferences. You will not be identified in any report or publication. A report will be made available through Breast Cancer Campaign and a lay summary will be sent to participants.

Who has reviewed the study?

This study has been checked by Northampton Research Ethics Committee, an independent group of people, to protect your safety, rights, wellbeing and dignity.

Any further queries?

If you have any questions or concerns about the study, you may contact the following organisations

For independent advice on participating in NHS research:
Patient Advice and Liaison Service (PALS) - 0207 188 8803

For independent advice about making a complaint:
South London Independent Complaints Advisory Service (ICAS) – 0300 456 2370

For information from the researchers:

Miss Zoë Moon: zoe.moon@kcl.ac.uk 0207 188 9324 (Principal Investigator)
Dr Lyndsay Hughes: lyndsay.hughes@kcl.ac.uk 0207 188 9779

CONSENT FORM Phase 2

Title of Project: Investigating how women with breast cancer view Tamoxifen

Name of researcher: Zoë Moon

Please initial each box

1. I confirm that I have read and understood the information sheet dated 20/10/2014 (v2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. I understand that data cannot be withdrawn once the results have been analysed and written up (December 2016). ☐

3. I understand that relevant sections of my medical notes may be looked at by the research team and that research data collected during the study may be looked at by individuals from King's College London, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study. ☐

5. I agree to be contacted in the future to complete follow up questionnaires. ☐

6. I agree to be contacted in the future about a follow up intervention study. ☐

……	……
Patient's name	Patient's signature
Date: ……	
……	……
Researcher's name	Researcher's signature
Date: ……	

Please provide your contact details below.

Name: ……

Telephone number: ……..

Address: ……

……

……

……

Email address: ……

If you are in your first year of treatment, we would like to send you follow up questionnaires at 3, 6 and 12 months' time. Please specify how you would like to receive the questionnaire:

I would prefer to receive the questionnaire in the post ☐

electronically (e-mail) ☐

Your contact details will be kept separately from your data and will be destroyed once the research is over.

Please keep my contact details on file to send me a summary of the results: Yes ☐

No ☐

Thank you for your participation.

QUESTIONNAIRE PACK

Screening questions

The following questions will determine if you are eligible to take part in the study. Please complete these before moving to the next set of questions. Circle the correct answer.

1. Are you female?

   YES NO

2. Are you aged 18 or over?

   YES NO

3. Have you been diagnosed with primary breast cancer?

   YES NO

4. Have you been prescribed Tamoxifen?

   YES NO

If you have answered yes to all the above questions then you are eligible to complete the rest of the questionnaire. When you are ready to complete the questionnaire, please continue and answer the remaining questions.

We are interested to find out your experiences since being prescribed Tamoxifen, even if you have stopped taking it.

Thank you for your time.

Please complete the following questions by ticking the box for the most appropriate answer.

1. **What is your date of birth (DD/MM/YY)? …….**

2. **What is your ethnic group? Choose one option that best describes your ethnic group or background.**

White - English / Welsh / Scottish / Northern Irish / British		White – Irish	
White - Gypsy or Irish Traveller		Any other White background	
White and Black Caribbean		White and Black African	
White and Asian		Any other Mixed / Multiple ethnic background	
Indian		Pakistani	
Bangladeshi		Chinese	
Any other Asian background		African	
Caribbean		Any other Black / African / Caribbean background	
Arab		Any other ethnic group	

3. **What is your relationship status?**

Single		Married	
Widowed		Co-habiting	
Separated / Divorced			

4. **Which of the following best describes your current job status?**

Employed full time		Employed part time	
Homemaker		Unemployed (unrelated to breast cancer)	
Unemployed/Retired (as a result of breast cancer)		Retired	
Other			

5. **How old were you when you left full time education?**

6. **How often have you visited your GP for any reason in the last four weeks?**

7. **When were you diagnosed with breast cancer (MM/YY)? …….**

8. **What stage was your breast cancer at diagnosis? (please tick the most appropriate answer)**

Stage 1 (tumour was 2cm or smaller and had not spread to lymph nodes)	
Stage 2 (tumour was between 2 – 5cm and / or the lymph nodes in the armpit were affected)	
Stage 3 (tumour was between 2 – 5cm and may be attached to structures in the breast. The lymph nodes in the armpit were affected)	
Stage 4 (the cancer had spread to other parts of the body)	
Unsure	

9. **What was the size of your breast cancer tumour?**

Under 2cm		Larger than 5cm	
Between 2cm – 5cm		Unsure	

10. **What treatment for breast cancer have you received?**

Lumpectomy (surgery to remove the cancerous lump)	
Single Mastectomy (surgery to remove the whole breast)	
Double Mastectomy (surgery to remove both breasts)	
Chemotherapy (the use of anti-cancer drugs to kill the cancer cells)	
Radiotherapy (the use of controlled radiation to kill cancer cells)	

11. **When did you complete surgery / radiotherapy / chemotherapy (MM/YY)?**

……

12. **Was your breast cancer Oestrogen positive (ER+)? This means the breast cancer cells have oestrogen receptors.**

Yes		No	
Unsure			

13. What was your menopausal status when diagnosed with breast cancer?

Pre-menopausal (no change in your patterns of periods)	
Menopausal (irregular periods)	
Post-menopausal (no period for 12 months)	
Unsure	

14. When were you first prescribed Tamoxifen (MM/YY)? If you cannot remember exactly, please write a rough estimate.

.....

15. What kind of healthcare professional prescribed you Tamoxifen?

16. Were you prescribed Tamoxifen for five or ten years?

17. Have you had any follow up appointments since being prescribed Tamoxifen?

Yes – GP		Yes – Consultant	
Yes – Nurse		No	

18. What is your current Tamoxifen dosage?

10mg		20mg	
40mg		Unsure	

19. Have you been switched from Tamoxifen to a different hormone therapy to prevent the risk of recurrence?

No		Yes – Anastrozole (Arimidex)	
Yes – Letrozole (Femara)		Yes – Exemestane (Aromasin)	
Yes – Goserelin (Zoladex)		Yes – Other	

20. Do you have any other medical conditions (e.g. asthma)?

Please list below:

Please read the following statements and tick the box to demonstrate the extent to which you agree or disagree with each statement. We are interested in your opinions and there are no right or wrong answers.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Tamoxifen disrupts my life					
Having to take Tamoxifen worries me					
I sometimes worry about becoming too dependent on Tamoxifen					
Tamoxifen is a mystery to me					
I sometimes worry about the long term effects of Tamoxifen					
My life would be impossible without Tamoxifen					
My health in the future will depend on Tamoxifen					
Without Tamoxifen I would be very ill					
Tamoxifen prevents me from becoming worse					
My health, at present, depends on Tamoxifen					

Emotions play an important part in most illnesses. This questionnaire is designed to help us know how you feel. Read each item and circle one of the replies below each item which comes closest to how you have been feeling during the past week. Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response.

1. I feel tense or 'wound up':

0 Most of the time
1 A lot of the time
2 From time to time, occasionally
3 Not at all

2. I still enjoy the things I used to enjoy:

0 Definitely as much
1 Not quite as much
2 Only a little
3 Hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen:

0 Very definitely and quite badly
1 Yes, but not too badly
2 A little, but it doesn't worry me
3 Not at all

4. I can laugh and see the funny side of things:

0 As much as I always could
1 Not quite as much as now
2 Definitely not so much now
3 Not at all

5. Worrying thoughts go through my mind:

0 A great deal of the time
1 A lot of the time
2 From time to time but not too often
3 *Only occasionally*

6. I feel cheerful:

0 Not at all
1 Not often
2 Sometimes
3 Most of the time

7. I can sit at ease and feel relaxed:

0 Definitely
1 Usually
2 Not often
3 Not at all

8. I feel as if I am slowed down:

0 Nearly all the time
1 Very often
2 Sometimes
3 Not at all

9. I get a sort of frightened feeling like 'butterflies' in the stomach:

0 Not at all
1 Occasionally
2 Quite often
3 Very often

10. I have lost interest in my appearance:

0 Definitely
1 I don't take as much care as I should
2 I may not take quite as much care as ever
3 I take just as much care as ever

11. I feel restless as if I have to be on the move:

0 Very much indeed
1 Quite a lot
2 Not very much
3 Not at all

12. I look forward with enjoyment to things:

0 As much as I ever did
1 Rather less than I used to
2 Definitely less than I used to
3 Hardly at all

13. I get sudden feelings of panic:

0 Very often indeed
1 Quite often
2 Not very often
3 Not at all

14. I can enjoy a good book or radio or TV programme:

0 Often
1 Sometimes
2 Not often
3 Very seldom

Many people find a way of using their medicines which suits them. This may differ from the instructions on the label or from what their doctor had said. Here are some ways in which people have said they use their medicines. For each statement, please tick the box which best applies to you.

	Never	Seldom	Some-times	Often	Always
I forget to use Tamoxifen					
I adjust the dosage of my Tamoxifen					
I stop using Tamoxifen for a while					
I decide to skip Tamoxifen doses					
I take fewer Tamoxifen tablets than prescribed to me					

	Yes	No
I have stopped taking Tamoxifen completely		

If you have stopped taking Tamoxifen completely, please explain why:

Please list the reason below:

Please read the statements and circle a number on the scale between 1 and 7. For example, circling 1 in the first statement indicates that you strongly agree.

People who are important to me think I should take Tamoxifen daily	*Strongly agree*	1 2 3 4 5 6 7	*Strongly disagree*
It is expected of me to take Tamoxifen every day	*Strongly agree*	1 2 3 4 5 6 7	*Strongly disagree*
I feel in control of whether I take Tamoxifen each day	*Strongly agree*	1 2 3 4 5 6 7	*Strongly disagree*
I am confident that I can take Tamoxifen daily	*Strongly agree*	1 2 3 4 5 6 7	*Strongly disagree*
My healthcare professionals think I should take Tamoxifen	*Strongly agree*	1 2 3 4 5 6 7	*Strongly disagree*
My family think I should take Tamoxifen	*Strongly agree*	1 2 3 4 5 6 7	*Strongly disagree*
I will try to take Tamoxifen daily over the next year	*Definitely will*	1 2 3 4 5 6 7	*Definitely will not*
How confident are you that you can overcome obstacles that stop you from taking Tamoxifen?	*Very confident*	1 2 3 4 5 6 7	*Not at all confident*
For me to take Tamoxifen daily will be…	*Very easy*	1 2 3 4 5 6 7	*Very difficult*
I intend to take Tamoxifen daily over the next year	*Definitely do*	1 2 3 4 5 6 7	*Definitely do not*
I feel under social pressure to take Tamoxifen	*Strongly agree*	1 2 3 4 5 6 7	*Strongly disagree*
Most people who have breast cancer take Tamoxifen every day	*Strongly agree*	1 2 3 4 5 6 7	*Strongly disagree*
Whether I take Tamoxifen or not is entirely up to me	*Strongly agree*	1 2 3 4 5 6 7	*Strongly disagree*
My friends think I should take Tamoxifen	*Strongly agree*	1 2 3 4 5 6 7	*Strongly disagree*
Having free time makes it easier to take Tamoxifen	*Strongly agree*	1 2 3 4 5 6 7	*Strongly disagree*
I want to take Tamoxifen daily over the next year	*Definitely do*	1 2 3 4 5 6 7	*Definitely do not*

How important is it for you to do what your friends think you should do?	*Extremely important*	1 2 3 4 5 6 7	*Extremely unimportant*
How important is it for you to do what your family think you should do?	*Extremely important*	1 2 3 4 5 6 7	*Extremely unimportant*
How important is it for you to do what your healthcare professional thinks you should do?	*Extremely important*	1 2 3 4 5 6 7	*Extremely unimportant*
I have free time	*Never*	1 2 3 4 5 6 7	*Frequently*

Taking Tamoxifen daily is….	*Good*	1 2 3 4 5 6 7	*Bad*
	Harmful	1 2 3 4 5 6 7	*Beneficial*
	Unpleasant	1 2 3 4 5 6 7	*Pleasant*
	Foolish	1 2 3 4 5 6 7	*Wise*
	Necessary	1 2 3 4 5 6 7	*Unnecessary*

Below is a list of statements that other people with your illness have said are important.
Please tick one box per line to indicate your response as it applies to the past 7 days.

	Not at all	A little bit	Somewh at	Quite a bit	Very much
I have hot flashes					
I have cold sweats					
I have night sweats					
I have vaginal discharge					
I have vaginal itching / irritation					

	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have vaginal dryness					
I have pain or discomfort with intercourse					
I have lost interest in sex					
I have gained weight					
I feel lightheaded (dizzy)					
I have been vomiting					
I have diarrhoea					
I get headaches					
I feel bloated					
I have breast sensitivity / tenderness					
I have mood swings					
I am irritable					
I have pain in my joints					

We would like to find out how informed you feel about your treatment. Please tick the box to indicate the extent to which you agree or disagree with the following statements:

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
I feel that I have received adequate information about Tamoxifen from my healthcare team.					
I fully understand why I have been prescribed Tamoxifen.					
I feel confident in my understanding of how Tamoxifen helps me.					
Whether or not I take Tamoxifen correctly each day will affect how it works.					

Listed below are a number of symptoms that you may or may not have experienced. **Please indicate by ticking the box in the first column if you have experienced any of these symptoms since your breast cancer.** If you have experienced a symptom**, please tick in any of the next three columns to indicate that you think the symptom** is related to your breast cancer, tamoxifen treatment or previous treatment.

		If you have experienced a symptom, please tick below to indicate if you think the symptom was related to your breast cancer, tamoxifen treatment or previous / other treatment. You may tick more than one box or leave the boxes clear.		
	I have experienced this symptom *since my breast cancer*	**This symptom is *related to my breast cancer***	**This symptom is *related to my Tamoxifen treatment***	This symptom is related to my *previous / other treatment*
Pain				
Upset stomach				
Change in sex drive				
Nausea				
Breathlessness				
Hot flushes				
Leg cramps				
Sore throat				
Weight loss / gain				
Loss of concentration				
Night sweats				
Fatigue				
Joint pain				
Vaginal dryness/ itchiness / discomfort				
Headaches				
Sleep difficulties				
Dizziness				
Loss of strength				
Feeling down				
Sore / itchy eyes				
Changes to periods				
Feeling lightheaded				

We are interested in views you hold currently about your breast cancer. **Please indicate how much you agree or disagree with the following statements about breast cancer by ticking the appropriate box.**

		Strongly disagree	Disagree	Neither agree not disagree	Agree	Strongly agree
IP1	My treatment has been effective in curing my breast cancer					
IP2	I no longer have breast cancer					
IP3	My breast cancer is cured					
IP4	I still see myself as having cancer					
IP5	I expect to have breast cancer for the rest of my life					
IP6	Tamoxifen has major consequences on my life					
IP7	I can't function normally whilst taking tamoxifen					
IP8	Taking tamoxifen has had an impact on those around me					
IP9	My work / social life has been affected by taking tamoxifen					
IP10	I struggle to cope with the side effects of tamoxifen					
IP11	There's a good chance my cancer will come back					
IP12	I expect to have a recurrence of cancer in the future					
IP13	I am extremely likely to have a recurrence					
IP14	The chance of my cancer coming back is low					
IP15	My breast cancer still has major consequences on my life					
IP16	My breast cancer currently does not have much effect on my life					
IP17	I still experience long lasting effects from my original treatment for breast cancer					
IP18	My breast cancer currently causes difficulties for those who are close to me (e.g. emotional difficulties)					
IP19	There are things I can do to stop the cancer coming back					

IP20	What I do has an influence on whether my cancer comes back					
IP21	There is nothing I can do to help my risk of recurrence					
IP22	My actions will have no effect on the risk of cancer coming back					
IP23	Tamoxifen treatment can reduce my risk of recurrence					
IP24	There is very little that can be done to stop the cancer coming back					
IP25	Taking tamoxifen will help stop the cancer coming back					
IP26	There is nothing that can help my risk of recurrence					
IP27	Tamoxifen is a mystery to me					
IP28	I understand how tamoxifen helps prevent cancer recurrence					
IP29	I don't understand how much tamoxifen can help me					
IP30	I have a good understanding of why I am taking tamoxifen					
IP31	I get depressed when I think about my risk of recurrence					
IP32	I worry about my risk of recurrence					
IP33	My risk of recurrence makes me feel angry					
IP34	When I think about the cancer coming back I get upset					
IP35	My risk of recurrence makes me feel afraid					

We are interested in what you think about possible causes or risk factors of recurrence. We are interested in your views and there are no correct answers. The factors below may or may not be related to cancer risk. **Please indicate by ticking the appropriate box to show the extent you agree or disagree that any of the factors below may influence your risk of recurrence.**

		Strongly Disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree
C1	Stress or worry					
C2	Runs in the family					
C3	A Germ or virus					
C4	Diet or eating habits					
C5	Chance or bad luck					
C6	Carcinogens in products (e.g. deodorant)					
C7	Pollution in the environment					
C8	My own behaviour					
C9	Exercise					
C10	Family problems or worries					
C11	My emotional state e.g. feeling down, lonely, anxious, empty					
C12	Ageing					
C13	Smoking (leave blank if not applicable)					
C14	Hormonal influence					

We are interested in how you feel about the following statements. Read each statement carefully and tick the box to indicate how you feel about each statement.

	Very strongly disagree	Strongly disagree	Mildly disagree	Neutral	Mildly agree	Strongly agree	Very strongly agree
There is a special person around when I am in need							
There is a special person with whom I can share my joys and sorrows							
My family really tries to help me							
I get the emotional help and support I need from my family							
I have a special person who is a real source of comfort to me							
My friends really try to help me							
I can count on my friends when things go wrong							
I can talk about my problems with my family							
I have friends with whom I can share my joys and sorrows							
There is a special person in my life who cares about my feelings							
My family is willing to help me make decisions							
I can talk about my problems with my friends							

Thank you for completing the questionnaire. Please return this to the researcher or post it using the stamped addressed envelope provided to you.

Appendix D

Supplementary material for IPQ-R modification study (chapter 5)

	Item on original IPQ-R	Item on modified IPQ-BCS
CURE BELIEFS	My breast cancer will last a short time	My treatment has been effective in curing my breast cancer
	My breast cancer is likely to be permanent rather than temporary	My breast cancer is cured
	My breast cancer will last for a long time	I no longer have breast cancer
	Breast cancer will pass quickly	I still see myself as having breast cancer
	I expect to have breast cancer for the rest of my life	I expect to have breast cancer for the rest of my life**
TAMOXIFEN CONSEQUENCES		*Tamoxifen has major consequences on my life*
		I can't function normally whilst taking tamoxifen
		Taking tamoxifen has had an impact on those around me
		My work / social life has been affected by taking tamoxifen
		*I struggle to cope with the side effects of tamoxifen***
RISK OF RECURRENCE		*There's a good chance my cancer will come back*
		I expect to have a recurrence of cancer in the future
		I am extremely likely to have a recurrence
		The chance of my cancer coming back is low
BREAST CANCER CONSEQUENCES	My breast cancer is a serious condition	I still experience long lasting effects from my original treatment for breast cancer
	My breast cancer has major consequences on my life	My breast cancer still has major consequences on my life
	My breast cancer does not have much effect on my life	My breast cancer currently does not have much effect on my life
	My breast cancer strongly affects the way others see me	Item removed
	My breast cancer has serious financial consequences	Item removed
	My breast cancer causes difficulties for those who are close to me	My breast cancer currently causes difficulties for those who are close to me (e.g. emotional difficulties)
PERSONAL CONTROL	There is a lot which I can do to control my symptoms	There are things I can do to stop the cancer coming back
	What I do can determine whether my breast cancer gets better or worse	What I do has an influence on whether my cancer comes back
	The course of my breast cancer depends on me	Item removed
	Nothing I do will affect my breast cancer	There is nothing I can do to help my risk of recurrence
	I have the power to influence my breast cancer	Item removed

TREATMENT CONTROL	My actions will have no effect on the outcome of my breast cancer	My actions will have no effect on the risk of cancer coming back
	There is very little that can be done to improve my breast cancer	There is very little that can be done to stop the cancer coming back
	My treatment will be effective in curing my breast cancer	Taking tamoxifen will help stop the cancer coming back
	The negative effects of my breast cancer can be prevented (avoided) by Tamoxifen treatment	Item removed
	Tamoxifen treatment can control my breast cancer	Tamoxifen treatment can reduce my risk of recurrence
	There is nothing which can help my breast cancer	There is nothing that can help my risk of recurrence
COHERENCE	The symptoms of breast cancer are puzzling to me	I understand how tamoxifen helps prevent cancer recurrence
	My breast cancer is a mystery to me	Tamoxifen is a mystery to me
	I don't understand my breast cancer	I don't understand how much tamoxifen can help me
	My breast cancer doesn't make any sense to me	Item removed
	I have a clear picture or understanding of my breast cancer	I have a good understanding of why I am taking tamoxifen
TIMELINE CYCLICAL	The symptoms of my breast cancer change a great deal from day to day	Item removed
	My symptoms come and go in cycles	Item removed
	My breast cancer is very unpredictable	Item removed
	I go through cycles in which my breast cancer gets better and worse	Item removed
	My breast cancer will improve in time	Item removed
EMOTIONAL REPRESENTATIONS	I get depressed when I think about my breast cancer	I get depressed when I think about my risk of recurrence
	When I think about my breast cancer I get upset	When I think about the cancer coming back I get upset
	My breast cancer makes me feel angry	My risk of recurrence makes me feel angry**
	My breast cancer does not worry me	Item removed
	Having breast cancer makes me feel anxious	Item removed
	My breast cancer makes me feel afraid	My risk of recurrence makes me feel afraid

Note. Items in italics are new and not on the original IPQ-R. ** indicates that the item was removed after the factor analysis.

Appendix E

Supplementary material for published paper in Chapter 6

Supplementary table showing associations between individual variables and intentional /unintentional non-adherence

	Intentional non-adherence	Unintentional non-adherence
Side effects total (r_b)	0.44**	0.14**
HADS distress (r_b)	0.37**	0.08
Informed (r_b)	-0.13*	-0.03
Social support (r_b)	-0.19**	-0.14**
Age (r_b)	0.01	-0.22**
Age left full time education (r_b)	0.01	.12**
Ethnicity: White vs. Other (Cramer's *V*)	0.02	0.09**
Relationship status: Single vs. with partner (Cramer's *V*)	0.01	0.13**
Job status: Employed vs. not employed (Cramer's *V*)	0.01	0.22***
Type of physician prescribed tamoxifen (Cramer's *V*)	0.11	0.12
Previous treatment: chemotherapy (Cramer's *V*)	0.02	0.08*
Previous treatment: radiotherapy (Cramer's *V*)	0.07	0.00
Previous treatment: single mastectomy (Cramer's *V*)	0.05	0.06
Previous treatment: double mastectomy (Cramer's *V*)	0.10**	0.00
Previous treatment: lumpectomy (Cramer's *V*)	0.04	0.01
Cancer stage (Cramer's *V*)	0.01	0.03
Menopausal status at diagnosis (Cramer's *V*)	0.04	0.11**
Comorbidities (r_b)	0.04	-0.08
Months since prescribed tamoxifen (r_b)	0.17**	0.21**
Duration of tamoxifen treatment (5 or 10 years) (Cramer's *V*)	0.07	0.11

*correlation is significant at the 0.05 level, ** correlation is significant at the 0.01 level, *** correlation significant at the 0.001 level

Appendix F

Baseline correlations between adherence and potential covariates (Chapter 8)

	Total non-adherence T1	Total non-adherence T2	Total non-adherence T3	Total non-adherence T4
Ethnicity (White vs. Black/Minority Ethnic)†	0.13 (*p*=.014)	0.11 (*p*=.050)	0.14 (*p*=.018)	0.03 (*p*=.670)
Age (r_b)	-0.11 (*p*=.099)	-0.23 (*p*=.002)	-0.14 (*p*=.061)	-0.20 (*p*=.010)
Relationship status (Single vs. with partner) †	0.06 (*p*=.279)	0.06 (*p*=.278)	0.05 (*p*=.438)	0.05 (*p*=.397)
Job status (Employed vs. not employed) †	0.11 (*p*=.053)	0.12 (*p*=0.37)	0.18 (*p*=.004)	0.19 (*p*=.003)
Age left full time education (r_b)	0.10 (*p*=.155)	0.17 (*p*=.018)	0.04 (*p*=.605)	0.02 (*p*=.778)
Cancer stage †	0.07 (*p*=.599)	0.16 (*p*=0.40)	0.11 (*p*=.333)	0.06 (*p*=.842)
Tumour size †	0.04 (*p*=.917)	0.11 (*p*=.309)	0.08 (*p*=.593)	0.06 (*p*=.844)
Type of physician prescribed tamoxifen †	0.08 (*p*=.927)	0.12 (*p*=.644)	0.15 (*p*=.358)	0.16 (*p*=.365)
Previous treatment: chemotherapy †	0.10 (*p*=0.58)	0.14 (*p*=.013)	0.09 (*p*=.150)	0.08 (*p*=.215)
Previous treatment: radiotherapy †	0.05 (*p*=.370)	0.05 (*p*=.338)	0.07 (*p*=.224)	0.08 (*p*=.232)
Previous treatment: single mastectomy †	0.01 (*p*=.813)	0.01 (*p*=.914*)*	0.02 (*p*=.682)	0.04 (*p*=.569)
Previous treatment: double mastectomy †	0.03 (*p*=.539)	0.10 (*p*=0.09)	0.01 (*p*=.828)	0.04 (*p*=.531)
Previous treatment: lumpectomy †	0.00 (*p*=.997)	0.01 (*p*=.891)	0.06 (*p*=.327)	0.07 (*p*=.282)
HR status †	0.05 (*p*=.700)	0.12 (*p*=0.94)	0.14 (*p*=.058)	0.05 (*p*=.696)
Menopausal status at diagnosis †	-0.80 (*p*=.152)	0.11 (*p*=.064)	0.09 (*p*=.154)	0.16 (*p*=.013)
Months since prescribed tamoxifen (r_b)	0.07 (*p*=.297)	-0.00 (*p*=.960)	-0.03(*p*=.664)	-0.01 (*p*=.920)
Duration of tamoxifen treatment (5 or 10 years) †	0.08 (*p*=.844)	0.15 (*p*=.213)	0.14 (*p*=.376)	0.20 (*p*=.076)
Number of follow up appointments †	0.17 (*p*=.041)	0.07 (*p*=.822)	0.08 (*p*=.802)	0.16 (*p*=.194)
Brand of tamoxifen †	0.12 (*p*=.223)	0.09 (*p*=.517)	0.12 (*p*=.287)	0.13 (*p*=.267)
Comorbidities (r_b)	-0.08 (*p*=.273)	-0.06 (*p*=.459)	0.01 (*p*=.891)	-0.03 (*p*=.766)
Social support (r_b)	-0.18 (*p*=.011)	-0.14 (*p*=0.47)	-0.19 (*p*=.013)	-0.20 (*p*=.012)
Side effects total (r_b)	0.01 (*p*=.153)	0.05 (*p*=.458)	0.20 (*p*=.009)	-0.20 (*p*=.012)
Distress (r_b)	0.12 (*p*=0.83)	0.12 (*p*=.103)	0.31 (*p*<.001)	0.26 (*p*=.001)
Informed (r_b)	-0.07 (*p*=.282)	-0.10 (*p*=.179)	-0.15 (*p*=.048)	-0.00 (*p*=.318)

† Indicates that Cramer's *V* was carried out to assess association.

Appendix G

Sensitivity analysis using lower MARS cut off (Chapter 8)

Table 1. Univariate LGM results for linear and quadratic functions

Model	Loglikelihood	BIC	Slope factor	Quadratic factor
Linear	-447.87	924.96	-0.08 (*p*=.426)	
Quadratic	--442.00	936.59		0.10 (*p*=.143)

Table 2. Non-adherence rates at each time point

Time-point	% non-adherent
T1	14%
T2	17%
T3	17%
T4	23%

Table 3. Bivariate associations between covariates and intercept / slope

Variable	Effect on intercept (OR)	Slope	Effect on slope
Ethnicity (black/minority ethnic)	3.34 (*p*=.157)	-0.09	0.11 (*p*=.617)
Job (employed)	1.93 (*p*=.262)	-0.20	0.15 (*p*=.221)
Menopausal status (post-menopausal)	1.46 (*p*=.479)	0.02	-0.19 (*p*=.089)
Chemotherapy	2.40 (*p*=.094)	-0.07	-0.05 (*p*=.659)
Age	0.98 (*p*=.391)	0.38	-0.01 (*p*=.137)
Months since prescribed tamoxifen	1.07 (*p*=.318)	-0.02	-0.01 (*p*=.460)
Distress	1.11 (*p*=.002)	-0.37	0.01 (*p*=.134)
Social support	0.72 (*p*=.097)	0.24	-0.05 (*p*=.143)
Side effect intensity	1.06 (*p*=.005)	-0.17	0.01 (*p*=.215)
Necessity/concerns differential	0.79 (*p*=.001)	-0.04	-0.02 (*p*=.134)
Risk of recurrence	1.03 (*p*=.693)	-0.01	0.00 (*p*=.813)
Breast cancer consequences	1.15 (*p*=.057)	-0.16	0.01 (*p*=.512)
Personal control	0.96 (*p*=.706)	0.22	-0.02 (*p*=.207)
Treatment control	0.85 (*p*=.160)	0.30	-0.02 (*p*=.235)
Coherence	0.78 (*p*=.006)	-0.01	-0.00 (*p*=.834)
Emotional representations	1.08 (*p*=.172)	0.03	-0.01 (*p*=.535)
Cure	0.97 (*p*=.680)	0.13	-0.01 (*p*=.395)
Tamoxifen consequences	1.22 (*p*=.006)	-0.33	0.03 (*p*=.036)
Cause: health behaviour	1.18 (*p*=.612)	-0.05	-0.01 (*p*=.892)
Cause: psychological attributions	1.72 (*p*=.073)	-0.27	0.06 (*p*=.382)
Symptoms attributed to tamoxifen (identity)	1.15 (*p*=.014)	-0.07	-0.00 (*p*=.720)
Attitude towards tamoxifen	0.88 (*p*=.001)	0.26	-0.01 (*p*=.352)
Subjective Norm	0.66 (*p*=.086)	0.18	-0.04 (*p*=.326)
Perceived Behavioural Control	0.38 (*p*<.001)	0.37	-0.05 (*p*=.267)

Table 4. CSM variables as predictors of non-adherence

Variable	Slope	Effect on intercept (OR)	Effect on slope
	-0.45		
Menopausal status (post-menopausal)		1.79 (*p*=.299)	-0.16 (*p*=.096)
Chemotherapy		3.12 (*p*=.055)	-0.07 (*p*=.504)
Distress		1.06 (*p*=.212)	0.01 (*p*=.603)
Social support		1.03 (*p*=.886)	-0.04 (*p*=.349)
Side effect intensity		0.98 (*p*=.537)	0.00 (*p*=.626)
Necessity/concerns differential		0.84 (*p*=.013)	-0.02 (*p*=.195)
Breast cancer consequences		0.94 (*p*=.435)	-0.01 (*p*=.431)
Coherence		0.94 (*p*=.496)	0.03 (*p*=.128)
Tamoxifen consequences		1.02 (*p*=.812)	0.05 (*p*=.018)
Cause: psychological stress		1.13 (*p*=.675)	0.01 (*p*=.931)
Symptoms attributed to tamoxifen		1.09 (*p*=.238)	-0.04 (*p*=.034)

Table 5. TPB variables as predictors of non-adherence

Variable	Slope	Effect on intercept (OR)	Effect on slope
	0.44		
Menopausal status (post-menopausal)		2.62 (*p*=.109)	-0.21 (*p*=.023)
Chemotherapy		2.98 (*p*=.073)	-0.12 (*p*=.167)
Distress		1.06 (*p*=.243)	0.01 (*p*=.559)
Social support		0.83 (*p*=.395)	-0.02 (*p*=.468)
Side effect intensity		0.98 (p=.566)	0.00 (*p*=.957)
Attitude towards tamoxifen		0.93 (*p*=.034)	-0.01 (*p*=.573)
Subjective Norm		1.19 (*p*=.510)	0.00 (*p*=.958)
Perceived Behavioural Control		0.40 (*p*=.002)	-0.03 (*p*=.571)

Appendix H

Patient documents used in intervention study

Patient Information Sheet

REC reference number: 193598

Feasibility and Acceptability of a Psychoeducational Booklet to Support Women who have been Prescribed Tamoxifen

We would like to invite you to take part in a research study conducted by King's College London and Guy's and St Thomas' Foundation NHS Trust.

The study will develop and trial a psychoeducational booklet aimed to support women who have been prescribed tamoxifen. Before you decide if you would like to take part, we will tell you why the research is being done and what it will involve for you.

One of our team will go over this information sheet with you and give you the opportunity to ask any questions. You will then be able to decide if you are interested in taking part in the study. If you would like more time to think about it, you can contact the researcher at a later date. The contact details are at the bottom of this form.

What is the purpose of the Study?

The purpose of the study is to test whether a psychoeducational booklet is acceptable and helpful for women who have been prescribed tamoxifen. The booklet will provide you with some information on what tamoxifen is and how it works, what side effects you may be experiencing, strategies for managing these side effects and tips for remembering to take tamoxifen. We would like to find out how the booklet made you feel, whether it was helpful and how it could be improved. The results from this study will help to develop the intervention further, allowing it to be rolled out to more women. The research is being conducted as part of a PhD at King's College London.

Why have I been asked to take part?

We have asked you to take part in the study because we are would like to test the intervention in a small group of women who have been prescribed tamoxifen but are finding it difficult to manage. There will be around forty women taking part in the study.

Do I have to take part?

It is up to you if you would like to join the study. If you are interested in taking part, we will ask you to sign a consent form. You are free to change your mind and to withdraw at any time. This will not affect your standard of care.

What will the study involve?

The study will involve you receiving the psychoeducational booklet for around 4 – 6 weeks. You will work your way through the booklet, completing one chapter per week. This will involve reading the information and completing exercises which will take about one hour for each chapter. You do not have to complete the whole chapter in one go, although we would like you to complete each chapter in the assigned week. One of the researchers will call you half way through the study to see how you are getting on. You will be asked to complete a series of questionnaires before starting the study and after you have completed the intervention. We will also contact you three months later to ask you to complete these questionnaires again.

You will also be asked to take part in an interview after the intervention to discuss your experiences and what you found helpful. This is to help us make any changes necessary to improve the booklet. The interview will be informal and can either take place face to face or over the telephone. We would like to record the interviews using an audio recorder so that the researcher can fully concentrate on what you are saying. The recordings will be deleted once they have been typed up.

Will I be reimbursed for my time?

We will reimburse you £20 for taking part in the intervention study. We will also reimburse you for any travel costs for attending an interview.

Will my information be kept confidential?

Your personal information will be kept confidential. The questionnaires will be inputted into a computer. Only the researchers will have access to the computer which will have a password to protect all confidential files. The interview will be recorded using an audio recorder, and the interview will be typed up. The recording will be typed up by an external company who have experience dealing with confidential data. The recording will be deleted and the typed up interview will be made anonymous. Any personal details or identifiable information will be removed and contact details will be stored separately in a locked filling cabinet. The data will be kept securely at King's College London. It will be destroyed five years after the research has finished. Your contact details will be destroyed as soon as the study has finished. Data cannot be withdrawn once the results have been analysed and written up (June 2017).

In the unlikely event of any risk such as self-harm or suicide risk, confidentiality will need to be broken. Your safety is very important. Both you and your clinical team will be made aware of the breach of confidentiality.

What are the possible disadvantages / benefits of taking part?

The risk of taking part is extremely minimal. You will need to read the booklet and complete a series of questionnaires. These questionnaires have been used previously and should not cause any distress. The booklet has been developed alongside feedback from patient representatives and therefore should not cause any harm. It is designed to support

you through your treatment and therefore you should benefit from taking part in the study. The information you provide us about the intervention will help us to develop the booklet further, which will help to support more women in the future.

What if there is a problem?

If the booklet raises any issues that you would like to discuss further with a health professional, the researcher will be able to put you in contact with the relevant person. You are free to withdraw from the study at any point. If you have a concern about any aspect of this study, you can speak to the Principal Investigator, or any other researchers involved in the study. The contact details are at the bottom of this sheet.

What will happen to the results of the research study?

The results of this study may be published in scientific journals and at medical and psychological academic conferences. You will not be identified in any report or publication. A report will be made available through Breast Cancer Now and a lay summary will be sent to participants.

Who has reviewed the study?

This study has been checked by London South East Research Ethics Committee, an independent group of people, to protect your safety, rights, wellbeing and dignity.

Any further queries?

If you have any questions or concerns about the study, you may contact the following organisations

For independent advice on participating in NHS research:
Patient Advice and Liaison Service (PALS) - 0207 188 8803

For independent advice about making a complaint:
South London Independent Complaints Advisory Service (ICAS) – 0300 456 2370

For information from the researchers:

Miss Zoë Moon: zoe.moon@kcl.ac.uk 0207 188 9324 (Principal Investigator)
Dr Lyndsay Hughes: lyndsay.hughes@kcl.ac.uk 0207 188 9779

CONSENT FORM

Title of Project: Feasibility and Acceptability of a Psychoeducational Booklet to Support Women who have been Prescribed Tamoxifen

IRAS number: 193598

Name of researcher: Zoë Moon

Please initial each box

1. I confirm that I have read and understood the information sheet dated 07/11/2016 (v3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. I understand that data cannot be withdrawn once the results have been analysed and written up (June 2017). ☐

3. I understand that relevant sections of my medical notes may be looked at by the research team and that research data collected during the study may be looked at by individuals from King's College London, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study. ☐

…… ……

Patient's name Patient's signature

Date: ……

…… ……

Researcher's name Researcher's signature

Date: ……

Please provide your contact details below.

Name: ……

Telephone number: ……..

Address: .....

…….

…….

…….

Email address: .....

Your contact details will be kept separately from your data and will be destroyed once the research is over.

Please keep my contact details on file to send me a summary of the results: Yes ☐

No ☐

Thank you for your participation.

SCREENING QUESTIONS

Please tick the answer which most applies to you.

1. Are you currently being prescribed tamoxifen for a diagnosis of primary breast cancer?

   ☐ **YES** ☐ **NO**

2. Are you currently undergoing chemotherapy or radiotherapy?

   ☐ **YES** ☐ **NO**

3. Are you over the age of 18?

   ☐ **YES** ☐ **NO**

4. Is your course of tamoxifen due to come to an end within the next four weeks?

   ☐ **YES** ☐ **NO**

5. Has your healthcare professional discussed switching you to another drug within the next four weeks?

   ☐ **YES** ☐ **NO**

6. Have you been diagnosed with Ductal Carcinoma In Situ (DCIS)?

   ☐ **YES** ☐ **NO**

7. Have you been diagnosed with secondary or metastatic breast cancer?

   ☐ **YES** ☐ **NO**

8. Has your doctor diagnosed you with depression?

   ☐ **YES** ☐ **NO**

Many people find a way of using their medicines which suits them. This may differ from the instructions on the label or from what their doctor had said. Here are some ways in which people have said they use their medicines**. For each statement, please tick the box which best applies to you.**

	Never	Seldom	Some-times	Often	Always
I forget to use Tamoxifen					
I adjust the dosage of my Tamoxifen					
I stop using Tamoxifen for a while					
I decide to skip Tamoxifen doses					
I take fewer Tamoxifen tablets than prescribed to me					

Appendix I

Intervention materials

KING'S College LONDON

A psychoeducational self-help manual for women who are taking tamoxifen

This booklet has been created to help support women who are taking tamoxifen. It has been created as part of research at King's College London, funded by Breast Cancer Now.

Zoe Moon, Professor Rona Moss-Morris, Professor Myra Hunter, Dr Lyndsay Hughes.

breast cancer now

KING'S College LONDON

breast cancer now

Activity booklet

Appendix J

T-tests and Chi-squared tests to compare participants who were lost to follow up to those who were retained in the feasibility study (Chapter 10)

	Retained (n=27) *M (SD)*	Did not complete full study (n=6) *M (SD)*	Difference between groups
Age	53 (6.3)	48 (SD=2.5)	$t(31)=1.69$, $p=.100$
Months since prescribed	34 (16.9)	43 (SD=52.8)	$t(5.2)=-0.41$, $p=.696$
Ethnicity (% white)	81%	83%	$X_2=0.02$ ($p=.885$)
Relationship status (% with partner)	59%	50%	$X_2=0.17$ ($p=.678$)
Job status (% employed)	89%	83%	$X_2=0.14$ ($p=.706$)
Age left full time education (% <16)	30%	17%	$X_2=0.42$ ($p=.519$)
Menopausal status at diagnosis (% pre-menopausal)	72%	83%	$X_2=0.33$ ($p=.569$)
MARS total	23.0 (1.6)	22.2 (1.0)	$t(31)=1.19$, $p=.244$
MARS intentional	19.3 (1.5)	19.2 (1.0)	$t(31)=0.26$, $p=.794$
MARS unintentional	3.7 (0.6)	3.0 (0.0)	$t(26)=5.59$, $p<.001$